

Interesting Insights from a Very Simple (Unicellular) Source

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The nicotinic acetylcholine receptors (nAChRs), ionotropic γ -aminobutyric acid (GABA) receptors (GABA_A and GABA_C), glycine receptors, and ionotropic serotonin receptors (5HT₃) all have a similar structure in which 5 membrane subunits of similar size and shape combine to form a transmembrane channel, something similar to the staves of a barrel. A large portion of each subunit extends out from the membrane into the extracellular fluid. This extracellular region contains a distinctive disulfide linkage, providing the "Cys-loop" moniker for these receptors.¹ Based on the species distribution, this superfamily of pentameric ligand-gated ion channels (pLGICs) was thought to be restricted to multicellular organisms. However, recently, pentameric proteins with large extracellular ligand-binding domains have been described in single-celled organisms.²⁻⁵ Although these channels lack the Cys-loop, their overall structure is remarkably similar to the pLGICs (see Fig. 1). Importantly, as demonstrated in the report by Weng et al.,⁶ the proton-activated currents of these channels are sensitive to both volatile anesthetics and propofol. But why should anyone care about the effects of anesthetics on a membrane protein from a Cyanobacteria (blue-green algae) *Gloeobacter* (aka GLIC)?

Over the past 2 decades, by a combination of membrane electrophysiology, molecular biology, and structural proteomics (radiograph diffraction and nuclear magnetic resonance), we have come to a far more detailed understanding of the molecular basis of membrane excitation. Based on their primary structure/amino acid sequence, the multihelix bundles forming the structure of ion channels were proposed. Subsequent radiograph diffraction structural studies by MacKinnon⁷ and Unwin^{8,9} have defined the structure of ion channels at the atomic level and delineated the precise molecular rearrangements that occur as ion channels open and close. In Figure 1, the structure of GLIC deduced from radiograph diffraction data^{4,5} is shown next to the structure of an nAChR.⁸ Although the primary amino acid sequence shows a modest similarity of <20% with nAChR subunits, the similarity in secondary and tertiary structures is remarkable. Equally remarkable is the fact that when these channels are expressed in cells, they are inhibited by remarkably low concentrations of various anesthetic agents.

In considering the pLGICs it is noteworthy that although similar in structure, they have distinct behaviors. For example, the lining of transmembrane helices vary significantly such that nAChRs and 5HT₃R transmit K⁺ and Na⁺ ions, whereas the GABA and glycine receptors transport Cl⁻; the former depolarize the cell whereas the latter (usually) hyperpolarize or stabilize the membrane potential. More importantly, whereas anesthetics inhibit certain types of nAChR channels,¹⁰ anesthetics favor the opening of glycine and GABA_A channels.¹¹ For more than a decade, specific amino acid mutations in the nAChR^{12,13} and the GABA_A¹⁴ receptor have been used to alter the sensitivity to volatile anesthetics and alcohol, and various investigators have inferred that specific binding sites exist on the channel protein. Are these differing anesthetic actions on various ion channels to be understood as actions of lipophilic molecules binding to distinct and randomly occurring amino acid sequences within each different membrane channel protein?

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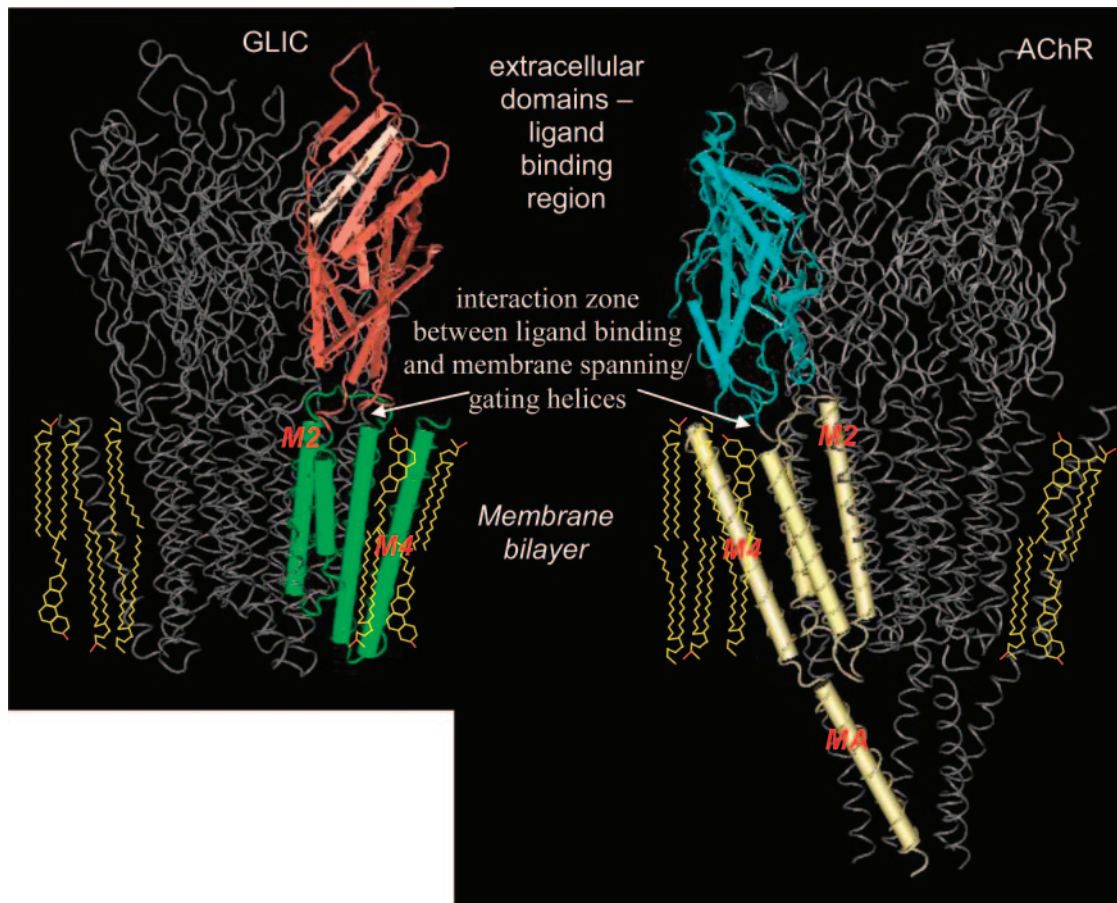


Figure 1. Structures of the *Gloeobacter* ligand-gated ion channel (GLIC, left) and a nicotinic acetylcholine receptor (nAChR, right) channel derived from radiograph diffraction and reproduced from the National Center for Biotechnology Information (code 3EHZ or 3EI0 for GLIC; code 2BG9 for nAChR; available at: <http://www.ncbi.nlm.nih.gov/sites/entrez?db=domains>). Each channel is composed of 5 subunits; 1 subunit in each channel is shown in cylinder (α -helix) and ribbon (β -sheet) format. The 5 M2 helices line the pore of the channel through which the ions pass. The M4 helix of each subunit actually extends most prominently into the lipid bilayer and is influenced by the order and structure of the lipid. The subunits of the AChR have an additional intracellular domain (MA) that forms a cage through which ions must pass. The linkage between the extracellular ligand-binding domain and the transmembrane bundle is mediated by salt bridges between these 2 regions (arrows). The approximate location of phospholipids and cholesterol, which constitute part of the bilayer, are shown in yellow.

While we know that these pLGICs have a major role in mediating anesthetic actions, what can these bacterial channel members tell us? Despite divergent behavior and very modest homology in amino acid sequence, the similarity in overall structure of these pentameric proteins suggests that some common mechanisms of action may exist. Part of the problem in attempting to find a common theme is that in all these channels, the binding of a simple molecule to a cleft between the subunit extracellular regions results in significant movement of transmembrane helices so that there is large enough space for ions to pass through. The connection between the ligand-binding site and the transmembrane helices occurs over significant molecular distance (more than the thickness of the bilayer). Although yet to be completely elucidated, the change in structure seems to be mediated not by a fixed link but via electrostatic interactions (salt bridges) between the extracellular domain and transmembrane α -helices.¹⁵ This interaction site is at the plane of the membrane interfacial region—at the

phospholipids head groups and polar portion of cholesterol. It is also in this region where tryptophan residues play an important role in anchoring the helical portion of the protein at the membrane surface.¹⁶ It seems more than coincidental that it is at the interfacial region of the membrane where volatile anesthetics reside.^{17,18}

Another emerging clue is that many membrane proteins do not merely float in a sea of nonspecific lipid but instead have specific lipid requirements. For example, the function of the AChR is markedly enhanced and in some sense seems to require the presence of cholesterol in the bilayer,^{19,20} whereas various lipids can alter channel function^{21,22} or drug actions.²³ Certain lipids are immobilized and remain tightly associated with pLGICs, while conversely membrane proteins also can cause specific organization of membrane lipids.²⁴ Interestingly, the steroid hormone progesterone has anesthetic potency and similar to anesthetics inhibits AChR channels but activates GABA_A channels. Anesthetically active steroids are

large and bulky molecules, and it is difficult to imagine that it would occupy the same site as a small halogenated ether.

The view that anesthetics are acting at either a lipid or protein site may end up being far too simplistic. One suggestion is that the mechanical properties of the membrane lipids can mediate alterations in channel function.^{25–27} Although such global properties of the membrane may contribute, we are beginning to understand that there is a complex and sophisticated interaction between the specific lipids with various segments of the membrane proteins. For example, the “soft” interaction of the ligand-binding region with the transmembrane helices may require certain interfacial lipids. The linkage between the extracellular ligand-binding domain with the ion-gating region might be altered by a change in a critical amino acid in the region, a change in the lipid, or by anesthetic disruption of lipid-protein interaction. It is not impossible that lipids and anesthetics might weaken the linkage in one pLGIC (AChR) but strengthen it in another (GABA).

But what of these bacterial channels? The ability to mutate these molecules and produce them in sufficient quantity to study their function and their structure make them an exciting model for our more complex glycine, GABA_A, nicotinic ACh, and 5HT₃ channels. Photoactivated anesthetics may be used to determine with which regions of the receptor the drugs interact. Their protein structure can be mutated to determine the location of amino acids critical for permitting anesthetic action, and whether lipids will indeed have a role. Study of GLIC and ELIC³ (*Erwinia chrysanthemi* LIC, yet another bacterial LIC) will begin to answer how our structurally simple agents produce their panoply of actions.

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The Hippocratic Paradigm in Medicine: Origins of the Clinical Encounter

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Progress in any scientific discipline depends on development of a language of inquiry: a vital linguistic requirement for the proper and unambiguous communication among scientists in their search for knowledge.¹ Observed phenomena, experimental results, notions, and technical terms can be clearly formulated, discussed, and debated but require a structure of precise and stable language.

A study of Medicine in the Classical Age (fifth century B.C.) indicates that the linguistic requirement in the development of a discipline of inquiry was not merely theoretical but a practical necessity. Essential to the advancement of science, including medicine, in the Greek world was that rival schools of physicians made conflicting claims regarding diseases, treatments, and the nature of medicine itself, supporting these claims using rhetorical schemes in oral or written form.¹⁻³ This unprecedented assembling of rational and systematic debates was marked by a transition from orality to the development of prose writing and set the stage for transforming medicine from traditional practice to a scientific discourse.^{4,5} Particular examples of disease led to general questions about sickness and health; questions seeking answers.^{2,4} These linguistic requirements bred the new language for the science (episteme) of medicine.

The Hippocratic Canon depicts the background underlying the systematic debate over medicine.^{6,7} It is the oldest collection of scientific and philosophical literature and thus provides a detailed view of Greek thought in its early stages. In the Canon, doctrines from different medical schools compete and occasionally conflict with each other, revealing an inconsistency of substance and style,⁶ acting to strengthen rather than weaken the value of the collection. Although the historical Hippocrates was not solely responsible for this upheaval, several of the texts acknowledged as genuine^{8,9} show that Hippocrates provided the momentum for this gradual paradigm shift¹⁰ from theoretical and religious accounts of philosophy and superstition to the evidence-based model of modern medicine.^{7,11,12}

In this issue of *Anesthesia & Analgesia*, Astyrakaki et al.¹³ provide a wealth of information about the Classical Age origin, etymology, and use of concepts defining theory and practice in our specialty. Among others, notions and terms such as anesthesia (*αναίσθησια*) and pain (*πονοσ*—*ponos*) are frequently encountered in the Hippocratic Canon and, either directly or through intimation, influence their modern usage by present day clinicians and scientists.

Hippocrates used the term anesthesia to denote loss of sensation as a result of disease or injury.¹³ In *Breaths*, the author* also associates seizure-induced loss of consciousness with insensibility to painful stimuli.¹⁴ Pedanius Dioscorides, a Greek physician living in Rome during the first century A.D., is recorded as the first person who, in his *De Materia*

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*Breaths is contained in the Hippocratic Canon and represents one of the most interesting examples of ancient medical philosophy. However, because of its philosophical style, modern scholars disagree in regard to its authenticity as a work of the historical Hippocrates.

Medica,¹⁵ makes explicit reference to the administration of mandrake-induced anesthesia to facilitate a surgical intervention. Oliver Wendell Holmes, a Professor of Anatomy and Physiology at Dartmouth College, is credited with “coining” anesthesia in a letter to William Morton on November 21, 1846.¹⁶ In this letter, Holmes states: “The state should, I think, be called ‘anesthesia.’ This signifies insensibility, more particularly (as used by Linnaeus and Cullen) to objects of touch.”^{16,17} It is acknowledged that William Cullen (1710–1790), a Scottish physician and chemist, explains anesthesia in his *Nosology*¹⁸ as the “impaired or lost sense of touch,” whereas the stance of Carl Linnaeus (1707–1778), a Swedish naturalist, physician, and father of modern taxonomy, is less clear and comes only from indirect sources.¹⁹ Both Cullen and Linnaeus, as well as Francois de Sauvages (1706–1767) in France,²⁰ supported definitions for the concept of anesthesia that were similar to the Hippocratic view (i.e., they regarded anesthesia as a result of disease or an injury) and definitely more limited than the direct account given by Dioscorides. As his writings and public stance show,^{12,21} Holmes was a true scholar of the history of medicine and greatly influenced by the Hippocratic way of thinking and practicing medicine. Interestingly, in *Medical Essays*,²² Holmes admits familiarity with the text of Dioscorides when he states: “I have welcomed Culpeper and Salmon to my bookcase as willingly as Dioscorides or Quincy . . .” It is thus likely that Holmes’ inspiration was a result of his close acquaintance with ancient Greek medical literature.

The semiology of pain is central to Hippocratic medicine. Following a holistic approach, Hippocrates did not treat pain as an isolated symptom or sign of disorder but rather as signifying the dynamic character of disease.²³ He was the first in Western medical tradition to use nouns (*πονός*—*ponos*—pain/chronic pain, *άλγος*—*algos*—pain/acute pain, *αλγημα*—*algema*—pain felt or caused/suffering, *οδυνη*—*odyne*—severe pain/labor pain), adjectives (*ισχυρός*—severe, *σφοδρός*—vehement, *οξύς*—sharp, *καταιγιζών*—rushing down like storm, *διαλειπών*—intermittent, *ασωδής*—attended with nausea), and synthetic words (*κεφαλαλγία*—cephalgia—headache, *καρδιαλγία*—kardialgia—heartburn) to characterize the different qualities, as well as sources of pain, avoiding at the same time an overclassifying taxonomy of the symptom. It has been suggested that the use of an extensive vocabulary to describe pain indicates an increased sensitivity toward the symptom²⁴; others argue that a paucity of terms indicates a precision of usage rather than sensitivity or insensitivity of the healers.²⁵ The Hippocratic physician benefited from a concise vocabulary of pain that was mainly based on patients’ description of symptoms, ensuring efficient patient–healer communication. Many of these descriptive Hippocratic terms found their way via all Western languages to modern medicine because they were precise and stable. These highly desirable qualities for technical scientific terms

originate from the fact that ancient Greek is no longer a conversational language and thus, unlike current spoken languages, is characterized by an established and stable semantic function.²⁶

Nevertheless, the study of phenomena with a distinctly emotional and psychological dimension, such as that of the lived experience of pain may benefit from the examination of specific cultural attributes.²⁷ Therefore, one studying pain in ancient societies always encounters a problem of translation.²⁸ This refers not only to pain terminology *per se* but also mostly to the existence, or not, of human universals—fundamental semantic primitives that can define the pain phenomenon across cultures, and time.^{29,30} The fact that the ancient world was acquainted with a number of anodynes (i.e., methods and substances to treat pain—*odyne*) known today creates the false impression that pain was both felt and relieved in the same way it is now. On the contrary, Hippocratic evidence does not support a primary role for pharmacopoeia in the treatment of pain, and, whenever used, the rationale behind its use is vague and does not appear to agree with contemporary standards.²⁸ Is there a metalanguage (i.e., language for the object language) of pain that can objectively analyze the distinctive properties of incommensurable^{10,31} theories and descriptions, since antiquity? This is an area of rigorous investigation in the field of linguistic psychology.

In conclusion, we applaud the authors for their interesting *ponema* (Greek word derived from *ponos*; meaning hard work) with ancient Greek medical literature. Although limited to concepts and terms mainly encountered in the specialty of anesthesiology, this lexicogrammatical assessment of the Hippocratic Canon is an important step in deciphering the origins of Western medicine.

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Plasma Exchange for Heparin-Induced Thrombocytopenia: Is There Enough Evidence?

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The perioperative management of patients who have a diagnosis of heparin-induced thrombocytopenia (HIT) with antibodies to heparin platelet factor 4 (anti-HPF4) and require cardiac surgery with cardiopulmonary bypass (CPB) has challenged clinicians for many years. Heparin has been administered to millions of patients since the first use of CPB to provide predictable and reliable anticoagulation, and to prevent blood from clotting in the extracorporeal circuit. There are numerous advantages of heparin for CPB over currently available alternative anticoagulants, including: 1) familiarity among practitioners; 2) ease of administration; 3) validated anticoagulant monitoring; 4) wide-ranging anticoagulant actions, including platelet inhibition; 5) availability of a reliable reversal agent; and 6) low cost.

Although off-label use of direct thrombin inhibitors (DTIs) was initially proposed as a potential solution for patients with anti-HPF4 requiring urgent cardiac surgery with CPB, use of a potent, irreversible anticoagulant likely increases the risk of life-threatening bleeding. There may also be increased risk of clotting, because there is limited experience in monitoring anticoagulation and in guiding appropriate dosing of DTIs during CPB. The bleeding risk may be amplified in certain patients, such as those having repeat cardiac surgery, complex surgeries, ventricular assist device insertions, and heart transplants. Such patients are typically at high risk for excessive bleeding based on both surgical factors and comorbidities such as hepatic and renal dysfunction, and they are often the patients who have anti-HPF4 when they present for surgery, having been exposed to heparin within the preceding 100 days.¹

The concern of excessive bleeding with the use of DTIs was initially illustrated in the case report by McDonald et al.² who described life-threatening (i.e., at 4 L/h) and unresponsive bleeding after a patient received r-hirudin anticoagulation for CPB. Even the use of the shorter half-life DTI, bivalirudin, in patients at low risk for bleeding can be associated with substantial bleeding in a subset of susceptible patients. For example, 6 of 98 patients enrolled in the Evolution-On Study who received bivalirudin had blood loss that exceeded 2.5 L in the first 24 postoperative hours compared with 58 patients who received unfractionated heparin and did not display this degree of blood loss.³ However, these findings have not been consistently observed as illustrated in a recent analysis of 115 patients who received bivalirudin anticoagulation for CPB and who did not develop excessive bleeding.⁴ We have also observed thrombosis in the venous reservoir despite adequate blood bivalirudin levels, which has prompted us to minimize hemostatic system activation by avoiding retransfusion of cardiotomy blood when we use a DTI for CPB. Nevertheless, until a reversal agent is commercially available for any current or emerging alternative anticoagulant to heparin, potential solutions need to be investigated to provide clinicians with alternatives to prevent development of life-threatening bleeding or clotting within the CPB circuit, which may occur with current alternatives, especially in patients who are at high risk for excessive bleeding. The article in this issue of *Anesthesia & Analgesia*

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by Welsby et al.⁵ is noteworthy in that it provides additional data regarding an approach that may be helpful for the management of patients with anti-HPF4 and who are at increased risk for perioperative bleeding. These investigators expand our limited knowledge of the potential use of plasmapheresis as a means to remove the antibodies, as described previously in a case report.⁶

Plasmapheresis was originally performed experimentally in 1660 by Dr. Richard Lower on dogs. Subsequently, procedures were performed manually (i.e., manual withdrawal of whole blood with concurrent administration of replacement solutions) in humans in France in 1902 and in the United States in 1914. It was not until 1960 that Solomon and Fahey used plasmapheresis therapeutically and it evolved to an automated process. Although in theory any antibody-mediated illness should clinically respond to a lowering of antibody levels via plasma exchange therapy, this concept is not always the case. A clinical response sometimes depends on a number of variables such as the extent of organ damage as related to the degree of deposition of antibodies at the time of diagnosis (e.g., Goodpasture disease). The lack of response is also likely when the levels of pathologic antibodies within blood do not correlate with the levels in the affected target organ such as the central nervous system (i.e., lowering blood levels does not necessarily result in lower central nervous system levels). Nevertheless, plasmapheresis is an established and potentially lifesaving medical therapy for certain disease states, such as thrombotic thrombocytopenic purpura, myasthenia gravis, and for monoclonal and polyclonal gammopathies such as Waldenström macroglobulinemia. More recently, therapeutic plasmapheresis is being utilized to treat life-threatening rejection of solid organs mediated by donor-specific antibodies to ABO or human leukocyte antigen (HLA) proteins within target organs, especially in the settings of heart and lung transplantation.

Although plasmapheresis is generally well tolerated and is rarely associated with catastrophic complications, such as air embolus, anaphylaxis, and infection, it may be associated with mild reactions related to citrate or allergens within either the replacement solutions used (e.g., albumin or plasma) or the extracorporeal plasma exchange system (e.g., ethylene oxide antibodies). Potentially fatal acute complications related to blood product transfusion may occur when plasma is used as the replacement solution, including transfusion-related acute lung injury and anaphylaxis. Bleeding may be either precipitated or aggravated in susceptible patients because coagulation factors are typically reduced by 70%–80% whereas platelet count decreases variably by $10\text{--}60 \times 10^3/\mu\text{L}$ with each exchange procedure.

The effective early use of plasmapheresis for the management of HIT has been described by several investigators.^{7–10} Plasmapheresis has also been used as a rescue therapy in patients with HIT who are

refractory to routine therapy enabling mechanical reduction of antibody titers¹¹ or as a bridge for pharmacological immune suppression. Although there has been only 1 previous report of plasmapheresis to acutely reduce pathologic antibodies in a patient with anti-HPF4 undergoing cardiac surgery,⁶ the hypothesis that this intervention might be effective in preventing HIT with thrombosis (HITT) is biologically plausible. Lowering the level of pathologic antibodies should decrease the risk of thrombotic complications after heparin exposure in patients with anti-HPF4 based on 2 general concepts. First, a direct relationship has been noted between anti-HPF4 concentrations measured by either enzyme-linked immunosorbent assay (ELISA) absorbance values or by percentage release of radioactive serotonin via the serotonin release assay and the propensity to develop thrombotic complications. Second, other antibody-mediated diseases that improve with plasmapheresis, such as thrombotic thrombocytopenic purpura and myasthenia gravis, generally start to respond when antibody levels are still detectable but reduced by 60%–80%.

In their retrospective institutional review, Welsby et al. describe 11 patients with anti-HPF4 who were managed with plasma exchange during surgery and who received unfractionated heparin for CPB-related anticoagulation. The investigators found that their approach seemed to be effective with respect to a lack of perioperative complications related to HIT when their patients were reexposed to unfractionated heparin, albeit for a short period when the heparin was restricted to the CPB period. The authors also provide the readership with a reasonable assessment of the limitations of their report in their Discussion section. Nevertheless, there are still several unanswered questions regarding their analysis and the potential usefulness of intraoperative plasmapheresis for the management of patients with HIT or HITT. Strikingly, only 2 of their 11 patients had platelet counts $<100 \times 10^3/\mu\text{L}$ at the time of their surgery, and although there were no obvious thrombotic complications, 8 of the 11 patients had postoperative thrombocytopenia with platelet counts $<100 \times 10^3/\mu\text{L}$. Ten of eleven patients displayed a postoperative decrease in platelet count, and, although thrombocytopenia is common after CPB, it is impossible to exclude ongoing HIT as a contributing factor in this cohort. It would have been extremely useful to have measured the antibody titers during the postoperative interval to examine this issue.

It is intriguing that the authors observed a 50%–84% reduction in antibody ELISA absorbance values with the majority (i.e., 8 of 11) of the patients having absorbance values below the lower limits of normal after a single 1.3 volume plasma exchange procedure as illustrated in their Figure 1. This result is quite impressive because a typical 1.5 volume exchange transiently reduces most protein levels by 78%, whereas five 1.5 plasma volume procedures are generally required to reduce antibody levels by 90%, as a

result of redistribution of the antibody from the extracellular space because 55% of immunoglobulin (Ig)G antibodies reside in the extracellular space. The authors did not note the time period for their postprocedure ELISA measurements, which would help elucidate a plausible explanation for their findings of substantially reduced ELISA absorbance values. If measurements were obtained in the initial postoperative period, a substantial reduction in anti-HPF4 values would be expected based on the impact of CPB-related hemodilution and/or volume replacement in the setting of intraoperative bleeding, which would result in further elimination or reduction of these antibodies.

Other important unresolved questions with this report involve the postoperative platelet count profiles of these patients and the management this series of patients received. In their Figure 2, the authors illustrate that most patients in their series had a prolonged platelet recovery period after surgery (i.e., 7–10 days). It is uncertain whether this was related to reemergence of antibody titers or to ongoing and accelerated platelet consumption in the first week related to endothelialization of the implanted left ventricular assist devices. Although the authors also mention that a subset of patients received postoperative plasmapheresis on the basis of either a suspicion of HIT or for prevention of graft rejection related to anti-HLA antibody profiles, they neglect to detail how many patients received this therapy and how many procedures were required. This is relevant because the lack of HIT-related thrombotic complications may have been secondary to the therapeutic effects of further plasma exchange therapy in the postoperative period. This leads us to the question of what should be done in the postoperative period to monitor and treat these patients. Although a subset of patients in this series ($n = 4$) was treated postoperatively with anticoagulants that are not implicated in the generation of anti-HPF4, for reasons other than suspicion of HIT, it would have been helpful to follow anti-HPF4 ELISA absorbance and/or serotonin release assay values serially to determine whether ongoing anticoagulant therapy would have been indicated based on theoretical risk of HITT. Perhaps one can also make the argument that anti-HPF4 antibody levels should be monitored postoperatively to identify whether the brief heparin exposure resulted in an increased immune response and on that basis to identify patients who would theoretically benefit from further plasmapheresis procedures as well.

Although we are left with some unanswered questions, the investigators should be congratulated for examining this treatment paradigm. What we now need is to perform further, more controlled analyses and perhaps even small, randomized trials to examine the clinical utility of this approach and to extend at least the monitoring, and perhaps the treatment period, into the postoperative period. More sophisticated monitoring methods, such as the serotonin release assay, should be included to confirm the

diagnosis of HIT and better define potential thrombotic risk. Controlled studies might shed more light on the potential benefit of plasmapheresis in the perioperative management of patients with anti-HPF4, HIT, and HITT. In the meantime, we are left with suggestive evidence that this approach may be helpful in reducing the risk of life-threatening bleeding and perhaps thrombosis in this high-risk patient population. We should also consider further investigation of other alternative approaches involving either use of short-acting platelet inhibitors such as prostacyclin analogues^{12–14} or short-acting IIb/IIIa receptor inhibitors such as tirofiban.^{15,16}

GLOSSARY

Heparin-induced thrombocytopenia (HIT): a clinical syndrome that involves a decrease in platelet count, usually exceeding 30% from baseline, which occurs after exposure to unfractionated or low-molecular-weight heparin and is not attributable to another cause of thrombocytopenia.

Heparin-induced thrombocytopenia and thrombosis (HITT): HIT that is complicated by arterial or venous thrombosis.

Anti-HPF4 antibodies: antibodies to the heparin platelet factor 4 complex, which are usually immunoglobulin (Ig)G class antibodies.

ELISA for anti-HPF4 antibodies: enzyme-linked immunosorbent assay screening test for all (i.e., IgG, IgM, IgA, etc.) or subtype specific (i.e., IgG) anti-HPF4 antibodies, including those that cause HIT (i.e., IgG) and those that do not.

Serotonin release assay (SRA): serotonin release assay is a functional test that determines whether a patient's plasma cause release of radio-labeled serotonin from donor platelets when they are exposed to unfractionated heparin. The SRA may be used to confirm (i.e., in the setting of a high pretest probability and a negative ELISA result) or exclude (i.e., in the setting of a low pretest probability with a positive ELISA result) the diagnosis of HIT.

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How Do We Bridge the Gap?

Andrew Herlich, DMD, MD, FAAP

The article by Costa et al.¹ in this issue of *Anesthesia & Analgesia* addresses the lack of knowledge and biases that anesthesiologists have toward dentists who provide sedation for their patients. The authors demonstrate through survey-based research that anesthesiologists are largely unaware of the sedation needs of dental patients. Ironically, the data in this article point to the fact that those anesthesiologists who work more closely with dentists actually have a greater bias than those who do not work with dentists. Although the sample size of the survey is restricted to a single region in Brazil, it points to issues that still exist in the United States today; anesthesiologists believe that dentists have no business sedating patients for dental procedures, with the possible exception of oral surgeons. Some anesthesiologists may be aware of the need for sedation and anesthesia for pain control to improve patient satisfaction with dental care. Anesthesiologists' safety concerns of the inadequacy of dentists' knowledge and training have been buoyed by situations described by Goodson and Moore and Coté et al. Goodson and Moore² described a pediatric dental patient's demise due to polypharmacy that included a combination of opiates, antiemetics, sedatives, and local anesthetics. Coté et al.³ demonstrated that there were failures to rescue dental patients from a level of sedation that was deeper than intended. Despite increasing regulatory efforts by many states to improve patient safety in dental offices, adverse outcomes still occur. However, we cannot be too smug about this issue; such untoward events also occur in physicians' offices, wherein the anesthesia care providers have more comprehensive training than many dentists.

Anesthesiologists are faced with an ongoing dilemma. Should they help educate dentists about sedation and anesthesia? If the answer is yes, then how can they help educate dentists about sedation and administration of anesthesia to dental patients and still feel comfortable that the caregivers are promoting patient safety? Anesthesiologists must be part of the educational process at all levels in order to convince themselves, as well as the public, that patient safety is the paramount concern. The American Dental Association (ADA) established "Guidelines for Teaching Pain Control and Sedation to Dentists and Dental Students" in 2007 with the help of the American Society of Anesthesiologists liaison to the ADA.⁴ These guidelines are quite specific in both content and hours of instruction. As the patients' level of sedation increases from simple anxiolysis to moderate sedation, and the anesthetic technique progresses from inhalation of nitrous oxide and enteral sedation to parenteral sedation, the guidelines increase in content and the instruction becomes more rigorous. The guidelines need to go further to convince anesthesiologists and the public that the dentists have received a level of education that promotes the highest standards of safety. Other means of education for graduate dentists have come from proprietary programs espousing the virtues of "sleep dentistry" by the administration of "stacked" doses of oral benzodiazepines. Anesthesiologists were not part of this program development. This form of enteral sedation has been embraced by many dentists because it increases access to care for individuals who might otherwise go without dental care. Irrespective of which program the dentist chooses, actual clinical or simulated contact is not very high. Many dental schools have created independent curricula that may include the ADA guidelines. However, 1 survey described dental school graduates' attitudes toward the

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curriculum as suboptimal at best. Furthermore, many students and graduate dentists thought that they were ill prepared to sedate patients in their offices, regardless of the training.⁵

The demands for sedation and anesthesia services exceed the number of providers by a wide margin. Several authors have shown that there is a great need for sedation and anesthesia for dental patients in both the pediatric and adult populations.^{6,7} Our anesthesiology colleagues in Scotland seemed to have a more practical and possibly enlightened attitude toward sedation for dental procedures by dentists.⁸ They recognize that anesthesiologists cannot meet all of the sedation and anesthetic needs but concede that dentists should be trained to use sedation in a safe manner. The article by Costa et al. briefly discusses the issue of cost containment. The costs of dental care delivered under general anesthesia are much greater than those of sedation in the dental office. This issue has been addressed by others; with future cost containment efforts, anesthesia for dental services in the hospital setting will inevitably be reduced.^{9,10}

The concept of anesthesiologists training dentists in the provision of sedation and anesthesia is not new. More than 30 yr ago, Klein et al.¹¹ addressed this issue. It was noted that there were insufficient numbers of dental schools that were training dentists in anesthesia and pain control outside the purview of oral surgeons. There were few specialists trained in dental anesthesia. Consequently, they proposed that resources from the National Institutes of Dental Research be used to support the training of dental specialists, who in turn would train other dentists at the dental school level and beyond. Anesthesiologists would train these dental specialists to safely administer sedation and anesthesia.¹¹ Predictably, there was a letter to the editor in response to the article by Klein et al., condemning the training of dentists by anesthesiologists in anything but local anesthesia. The author of the letter pointed to patient safety concerns as the reason why dentists should not be trained in anesthesia.¹² The condemning letter expressed a majority view of most anesthesiologists at that time. Klein et al. answered the letter to the editor and stated that the intent of training was not to establish a group of "... barely trained individuals who feel that they have the stamp of approval to administer general anesthesia in the dental office." The intent was to create highly trained clinicians who were also consummate educators. They would return to dental schools and create curricula that would educate dentists and dental students, who in turn would safely and rationally sedate their patients as solo practitioners.¹³

The needs have not changed much: anesthesiologists need to help educate their dental colleagues. There are many means and techniques to help fulfill

these goals. If hands-on patient care is not readily available, then high-fidelity simulation will be very useful in training dentists in these sedation and anesthesia skills. The article by Costa et al. underscores that we have a long way to go. To dispel the biases that are discussed in this article, anesthesiologists must be convinced that the dentists' training in sedation techniques require similar levels of competency as those required of anesthesiologists during anesthesia residency, and that the patient safety requirements are also similar. We have a unique opportunity to reduce the contention of Coté et al. that failure to rescue is the crux of the problem of patient safety. The patient cannot be rescued if the clinician fails to recognize that there is a problem. The only means of recognizing the problem is through a high-quality educational process that we as anesthesiologists can (and should) help steward. Future health care initiatives will undoubtedly create anesthesia "extenders" that attempt to span the gulf between those who need anesthesia care and the number of providers who are available. If we do not help bridge that gap, then we only have ourselves to blame if legislative initiatives create lower standards.

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Neuraxial Blockade in Patients with Spinal Stenosis: Between a Rock and a Hard Place

Terese T. Horlocker, MD

Although severe or disabling neurologic complications after neuraxial block are rare, an epidemiologic series suggests that the frequency of some serious complications is increasing.¹ The presence of new or progressive neurologic deficits necessitates prompt evaluation to detect potentially treatable sources of neurologic injury. In this setting, magnetic resonance imaging (MRI) is the preferred technique to diagnose spinal hematoma, epidural abscess, and mechanical trauma; acute spinal cord ischemia may be undetectable by conventional MRI. However, prior performance of a neuraxial technique may affect interpretation of the images. Radiologists must discern between benign “coincidental” findings, normal procedural-related changes, and those that represent pathologic processes. For example, spinal MRI findings in patients receiving continuous epidural analgesia may mimic those of epidural abscess (e.g., posterior epidural enhanced “lesion” with spinal cord compression) even in the absence of infection.² Misinterpretation of MRI findings may lead to unnecessary therapies, including surgery. Despite these implications, MRI after uneventful neuraxial techniques remains largely undefined. Previous investigations have involved single cases or small series.^{2,3}

In this issue of *Anesthesia & Analgesia*, Davidson et al.⁴ systematically characterized the MRI findings of 30 parturients, 15 of whom had undergone a combined spinal epidural technique, to define normal MRI appearance after uneventful epidural analgesia. MRIs were performed approximately 10 h after delivery. There were no significant fluid collections, hematomas, or compression of the thecal sac noted in any of the MRI studies. However, the presence of an injection track, abnormal soft tissue abnormalities, and/or epidural air allowed the image readers to correctly identify which parturients had undergone a neuraxial technique in 93% of cases. The investigators concluded that the lack of pathologic MRI findings after uncomplicated epidural analgesia suggests that the presence of significant fluid collection or mass effect, in the setting of new neurologic deficits, warrants immediate intervention. This imaging study illuminates our understanding of the anatomic changes, as defined by MRI, induced by neuraxial block. Additional studies are needed to characterize the MRI findings in other patient populations, particularly those with preexisting pathology of the vertebral column, such as spinal stenosis. This knowledge is crucial in understanding the apparent increased risk of neurologic complications associated with neuraxial blockade in these patients.

Pathology of the spine has been proposed as a risk factor for complications after neuraxial techniques. Recent series and case reports support this hypothesis, although the mechanism of injury, ischemia, or neurotoxicity is unclear. An epidemiologic study evaluating severe neurologic complications after neuraxial block conducted in Sweden between 1990 and 1999 revealed some disturbing trends.¹ During the 10-yr study period, approximately 1,260,000 spinal and 450,000 epidural blocks (including 200,000 epidural blocks for labor analgesia) were performed. A total of 127 serious complications were noted, including spinal hematoma,³³ cauda equina syndrome/paraparesis,³⁶ meningitis,²⁹ and epidural abscess.¹³ The nerve

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damage was permanent in 85 patients. Fourteen of the patients had preexisting spinal stenosis. However, the spinal stenosis was known preoperatively in only 1 case; the remaining 13 cases were diagnosed in the subsequent investigation of the complication. Furthermore, in patients with spinal stenosis, the frequency of cauda equina syndrome and spinal hematoma increased with age. This large series suggests that the incidence of severe anesthesia-related complications is not as low as previously reported (the overall frequency was approximately 1:10,000) and preexisting spinal canal pathology may be a "neglected risk factor."¹ A 1-yr survey in France of nerve root and spinal cord injury after neuraxial block revealed 12 cases of severe and long-lasting complications, including 5 cases of spinal stenosis and 2 spinal arachnoid cysts.⁵ A growing number of case reports implicate severe asymptomatic spinal stenosis as a contributing factor in the occurrence or severity of nerve injury after neuraxial block.⁶⁻⁹ The majority of cauda equina cases involved epidural analgesia, suggesting an ischemic component (from mechanical compression of the cord by the infusate) to the injury.

Spinal stenosis is a narrowing of the spinal canal and neural foramina produced by age-associated changes in the disks and facet joints, including disk degeneration, facet joint capsule hypertrophy, infolding of the ligamentum flavum, and osteophyte formation.¹⁰ The mechanism by which spinal nerve root compression results in the signs and symptoms of spinal stenosis (back/leg radicular pain, usually without sensory or motor deficits, which is exacerbated with extension and alleviated flexion) has not been fully explained. However, both laboratory and clinical models correlate symptomatology to increases in intraspinal pressure.¹¹ An increase in mechanical pressure as low as 10 mm Hg may produce venous occlusion as well as reduce cerebrospinal fluid and blood flow, resulting in metabolic impairment of the nerve roots and spinal cord.¹² This is notable in that increases in epidural pressure are common in elderly patients undergoing epidural analgesia. In a classic investigation reported in 1967, Usubiaga et al.¹³ measured epidural pressures in 405 patients scheduled for elective surgery. In all patients, epidural injection of 10 mL of lidocaine produced an instantaneous increase in epidural pressure; peak pressures ranged from 5 to 65 cm H₂O (4 to 40 mm Hg). The highest pressures occurred in sitting patients. After injection, the pressure "normalized" within 2 min in patients younger than 50 yr. A slow rate of descent, with higher residual pressures, was reported in elderly patients. The pressure changes were transmitted to the intrathecal space at the same level. Finally, the authors correlated high epidural pressures with extent of block, which was interpreted as a "confinement of a larger amount of solution inside the epidural space" due to age-related changes. The effect of epidural injection on cerebrospinal fluid displacement was more recently assessed

by Takiguchi et al.¹⁴ who reported that injection of 10 mL of epidural saline 10 min after spinal anesthesia resulted in a spinal level 4 segments higher. In addition, serial epidural injections of 5 mL (to a total of 20 mL) resulted in a reduction in the diameter of the subarachnoid space to approximately 40% after the first injection and to 25% after the second injection. Further decreases were observed with the third and fourth injections. Although these effects may not be clinically significant in many patients, in combination with spinal stenosis, they may result in irreversible neural compromise. Essentially, the prolonged increase of epidural pressure may exacerbate preexisting pathology and increase the risk of nerve root ischemia. The ischemic effects may be further enhanced by the neurotoxicity of local anesthetic solution.

The relative risk of neuraxial blockade in patients with preexisting spinal canal pathology is unknown. In a series of 230 patients undergoing spinal anesthesia, the frequency of paresthesia during needle placement (20% vs 9%) or injection (16% vs 6%) was higher in patients with known lumbar spine pathology compared with those with normal spines.¹⁵ Importantly, although the elicitation of a paresthesia may increase the risk of postoperative persistent paresthesia, no patient developed transient or permanent nerve deficits. Conversely, the cases of cauda equina syndrome/paraparesis often occur after an uneventful neuraxial technique.^{1,7,8} A single study, for which only preliminary results are available, examined the overall success and neurologic complication rates among 937 patients with spinal stenosis or lumbar disk disease undergoing neuraxial block between 1988 and 2000.* Of these, 210 patients had a coexisting peripheral neuropathy in addition to their spinal cord pathology. Neurologic diagnoses were present 5 ± 6 yr; half of the patients had active symptoms at the time of the block. In addition, 207 patients had a history of spinal surgery before undergoing neuraxial block, although a large number of the procedures were simple laminectomies or discectomies. Ten patients (1.1%; 95% confidence interval 0.5%–2.0%) experienced new or progressive neurologic deficits when compared with perioperative findings. Although the majority of the deficits were related to surgical trauma or tourniquet ischemia, the neuraxial block was likely the primary etiology in 4 patients.

The preliminary nature of these data warrants care in their interpretation. Even more troubling are spontaneous cases of cauda equina syndrome that have occurred during general anesthesia in the absence of neuraxial block.¹⁶ Additional large series and imaging studies are required to quantify the risk and characterize the mechanism of severe neurologic complications after uneventful neuraxial (primarily epidural)

*Hebl JR, Horlocker TT, Schroeder DR. Neurologic complications after neuraxial anesthesia or analgesia in patients with preexisting spinal stenosis or lumbar disc disease. *Reg Anesth Pain Med* 2005;29:A89.

blockade and the additive or synergistic contribution made by preexisting spinal stenosis. Until then, we are between a rock and a hard place.

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The Risk-Benefit Profile of Aprotinin Versus Tranexamic Acid in Cardiac Surgery

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BACKGROUND: Aprotinin is superior to other antifibrinolytic drugs for preventing major blood loss after cardiac surgery but may also increase perioperative mortality. It remains unclear whether its risk-benefit profile differs among low-, moderate-, and high-risk cardiac surgical patients.

METHODS: In this retrospective single-center cohort study, we included 15,365 patients who underwent cardiac surgery with cardiopulmonary bypass from 2000 to 2008. Of these, 1017 received aprotinin (6×10^6 U) and 14,358 received tranexamic acid (50–100 mg/kg). Propensity score methods were used to create a matched-pairs cohort ($n = 1544$) that adjusted for important between-group differences. The influence of patients' risk status on aprotinin's association with in-hospital mortality, morbidity, and blood loss was measured.

RESULTS: In the matched set, aprotinin was only associated with increased acute kidney injury (>50% decrease in estimated glomerular filtration or dialysis; odds ratio 1.5; 95% confidence interval [CI] 1.1–2.1). Patients' risk status significantly influenced the associations of aprotinin with mortality, acute kidney injury, and massive blood loss (transfusion of ≥ 10 U of red blood cells or need for surgical reexploration). Among high-risk patients, the respective odds ratios were 0.6 (CI 0.3–1.0), 1.1 (CI 0.7–1.7), and 0.7 (CI 0.4–1.04), and among low- to moderate-risk patients, they were 1.5 (CI 0.9–2.7), 2.2 (CI 1.4–3.5), and 1.2 (CI 0.9–1.07) (Breslow-Day test for homogeneity of odds ratios between high-risk versus low- to moderate-risk patients: $P < 0.05$ for all 3 outcomes).

CONCLUSIONS: Aprotinin tends to have a better risk-benefit profile than tranexamic acid in high-risk, but not low- to moderate-risk, patients. Its use in high-risk cases may therefore be warranted.

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Impaired hemostasis is a major sequela of cardiac surgery with cardiopulmonary bypass (CPB), because it frequently leads to excessive blood loss and blood product transfusions and is linked to adverse outcomes.¹ Although its causes are multifactorial, a major

contributing factor is excessive fibrinolysis.² To alleviate this complication, physicians often administer drugs that inhibit fibrinolysis. Two types of these drugs are clinically available: lysine analogues (tranexamic acid and ϵ -aminocaproic acid) and serine protease inhibitors (aprotinin).² The lysine analogues act by reversibly binding to the lysine-binding site of plasminogen, thereby preventing its conversion into plasmin, a fibrin-degrading serum protease.³ Aprotinin also attenuates fibrinolysis by inhibiting the action of plasmin,³ but it does this more efficiently by forming reversible enzyme inhibitor complexes.⁴ Unlike the lysine analogues, aprotinin simultaneously inhibits other serine proteases, such as thrombin and kallikrein, thereby enhancing its hemostatic effects and conferring it antiinflammatory effects.^{5,6}

The relative risk-benefit profile of these drugs is controversial. Aprotinin has generally been considered to be clinically superior to the lysine analogues, particularly in complex, high-risk cases in which patients are more likely to develop profound coagulopathy and systemic inflammatory response syndrome.⁷ Recently, however, several observational studies^{8–10} and a randomized trial (Blood Conservation Using Antifibrinolytics in a Randomized Trial [BART])¹¹ have found that patients who receive aprotinin have

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higher morbidity and mortality than those who receive lysine analogues. Largely based on these new findings, the marketing approval for aprotinin was recently withdrawn in Europe and placed under severe restrictions in North America.

Very little of the current data, however, pertains to use in high-risk cases, which is where the benefits of aprotinin are most likely to outweigh its risks. Most studies limited their sample to coronary artery bypass graft (CABG) surgeries, which are generally low- to moderate-risk cases. Even in the BART trial, which aimed specifically to study high-risk cases,¹¹ complex or emergency surgeries were excluded or not enrolled; consequently, the study included predominantly moderate-risk patients. In our previous observational study,¹² we assessed the risk-benefit profile of aprotinin by comparing the outcomes of 449 patients who received aprotinin with 449 propensity score-matched patients who received tranexamic acid at an institution where aprotinin was preferentially used in high-risk cases. Because most high-risk patients at the institution received aprotinin during the study period, however, we were unable to find a suitable match for many of them. Our assessment, therefore, was also limited primarily to low- and moderate-risk patients.

Given the restrictions placed on aprotinin in 2007, we have since been using tranexamic acid in all of our cardiac surgical patients. Thus, we now have data on more high-risk patients who received tranexamic acid but would have previously received aprotinin. This change in practice provided us the opportunity to compare aprotinin with tranexamic acid across a wider spectrum of risk than in our previous study. Our hypothesis was that aprotinin would have a superior risk-benefit profile in higher-risk cardiac surgical cases.

METHODS

Patient Sample

After obtaining institutional ethics board approval, which waived the requirement for informed consent, consecutive patients, aged 18 yr or older, who underwent cardiac surgery with CPB from January 2000 to May 2008 at the Toronto General hospital, were included in this single-center cohort study. Patients who did not receive aprotinin or tranexamic acid and those who participated in the BART trial ($n = 144$) were excluded. For patients who were readmitted for additional operations requiring CPB during the study period, only data from their first admission were used.

Study Setting and Clinical Practice

A full range of adult cardiac surgery procedures is performed at the Toronto General Hospital, which is a quaternary-care teaching hospital affiliated with the University of Toronto. Clinical care during the study period was guided by previously described standardized guidelines.¹²

Until its use was restricted, institutional guidelines recommended that aprotinin (test dose followed by 2×10^6 U over 30 min after induction of anesthesia, 2×10^6 U in the pump prime, and 2×10^6 U infused over 4 h) be used in complex procedures requiring prolonged CPB support, >1 previous sternotomy, or endocarditis. All other patients were to receive 50–100 mg/kg (given over 5–10 min IV after induction of anesthesia) of tranexamic acid, with higher-risk patients receiving the higher dose. After aprotinin use was restricted, this tranexamic acid regimen was used in all patients undergoing CPB procedures.

Anticoagulation during CPB was achieved with heparin to maintain kaolin activated clotting time >480 s.

Data Collection

All perioperative data were prospectively collected in institutional databases, as has been previously described.^{12,13} Full-time research personnel blinded to the details of this study adjudicated all patient outcomes from patients' records. Quality assurance checks of the databases have consistently revealed a missing data rate of <2% and an error rate of <2%. Patients with missing values for variables used in the multivariable analyses were excluded.

Outcomes

Based on existing data, 3 outcomes were of primary interest: in-hospital death, acute kidney injury (based on the RIFLE¹⁴ criteria of >50% decrease in estimated glomerular filtration rate, calculated with the Cockcroft-Gault¹⁵ equation, using preoperative and highest creatinine concentration during the first week after surgery, or the need for initiation of dialysis after surgery), and massive blood loss (transfusion of ≥ 10 U of red blood cells or surgical reexploration).

Other measured outcomes included postoperative acute kidney failure requiring dialysis support, stroke (new persistent neurological deficit with radiological confirmation), myocardial infarction (new electrocardiogram changes plus elevated cardiac enzymes), and serious infections (sepsis or deep sternal infection).

Covariates

Measured perioperative variables that may have influenced aprotinin use or perioperative blood loss were examined. These included preoperative patient characteristics (demographics, important comorbidities, as well as preoperative creatinine, hemoglobin, platelet, and international normalized ratio of prothrombin time), surgery-related variables (surgeon, procedure, urgency, and CPB duration), and patients' large-volume red blood cell transfusion risk score, as determined by a previously validated risk score.¹⁶

Measure of Patients' Risk Status

The Toronto Risk Score regression formula was used to calculate each patient's predicted perioperative risk for major adverse events.¹⁷ This prediction

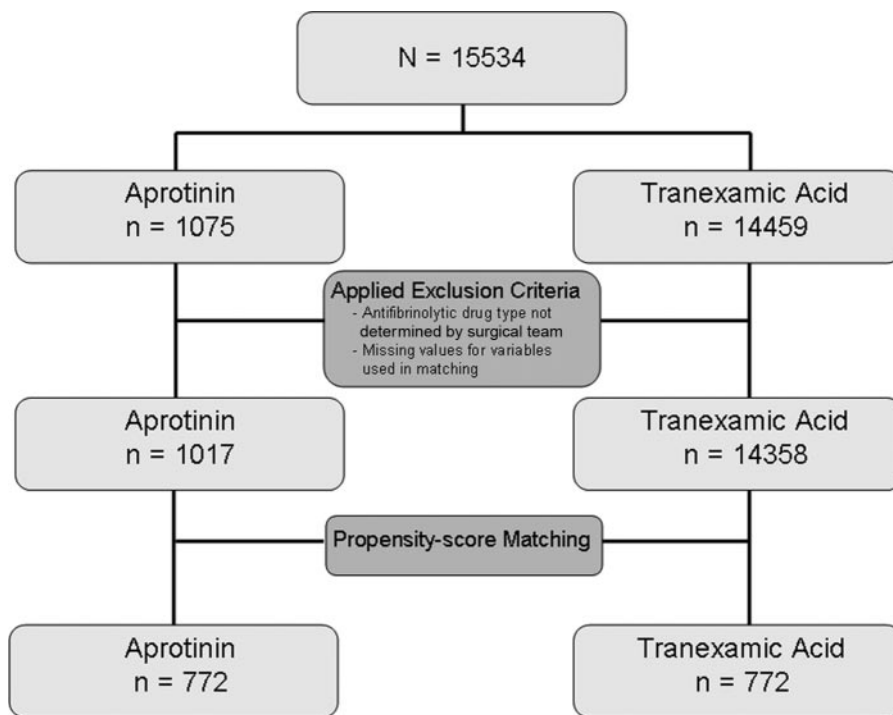


Figure 1. Patient flow diagram.

rule was used instead of better known ones, such as the EURO score,¹⁸ because it was developed (on patients who underwent surgery between 1996 and 2000) and validated (on patients who underwent surgery between 2000 and 2002) at our institution. It should, therefore, be more accurate than other scores for estimating the risk status of patients who undergo cardiac surgery at our institution. Details of the risk score are shown in the Appendix.

Statistical Analyses

Because treatment assignment was not based on random allocation, propensity score methods were used to match patients who received aprotinin to patients who received tranexamic acid.^{19,20} A propensity score for receiving aprotinin was estimated using a multivariable logistic regression model. All measured covariates (except for year of surgery) were considered for inclusion as predictor variables in this model (criteria for inclusion, $P < 0.2$). Each patient who received aprotinin was then matched to a patient who received tranexamic acid based on similar propensity scores (using a 5 → 1 computerized greedy-matching technique).²¹

The matched pairs were then compared on all measured covariates to determine whether the groups were balanced. Groups were considered to be balanced on a covariate if the standardized mean difference, which is the absolute difference of the group means as a percentage of their pooled SD, was $< 10\%$.¹⁹ If the model failed to achieve balance for any covariate that was not in the model, the covariate was forced into subsequent models. If balance was not achieved for a covariate that was in the model, the cross-products of that covariate with other clinically related

variables were included in subsequent models. This process was repeated until the propensity score derivation model resulted in matched groups that were balanced on all important covariates.²² The outcomes between these matched pairs were then compared using conditional logistic regression.¹⁹

The influence of patients' perioperative risk status on the relative risk-benefit profile of aprotinin and tranexamic acid was assessed by plotting the cubic spline function curves of the observed rates of mortality, acute kidney injury, and massive blood loss against the predicted risk for major adverse events (as calculated by the Toronto Risk Score regression formula)¹⁷ for matched patients according to type of drug received. The Breslow-Day²³ test for homogeneity of odds ratios was used to determine whether the effects of the drugs differed between high-risk and low- to moderate-risk subgroups.

Statistical analyses were performed using SASTM version 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 15,534 patients underwent cardiac surgery with CPB during the study period and received aprotinin or tranexamic acid. After application of the exclusion criteria, 15,365 patients were included in the study, 1017 (6.6%) of whom received aprotinin (Fig. 1). As can be seen in Table 1, there were many important prognostic differences between those who received aprotinin and those who received tranexamic acid. Most notably, aprotinin patients underwent more complex, high-risk surgeries requiring markedly longer CPB support than tranexamic acid patients.

Table 1. Comparisons of Selected Covariates and Outcomes in the Entire Sample and According to Antifibrinolytic Therapy

| Variables | Entire sample | | | Matched patients | | | Unmatched patients | |
|---|-------------------------|--------------------|------|------------------------|-----------------|-------|------------------------|--------------------|
| | Aprotinin (n = 1017) | TA (n = 14,358) | SMD | Aprotinin (n = 772) | TA (n = 772) | SMD | Aprotinin (n = 245) | TA (n = 13,586) |
| Age (yr) | 55 ± 17 | 63 ± 12 | 60% | 58 ± 16 | 58 ± 16 | 5.3% | 48 ± 17 | 63 ± 12 |
| Female | 35% (360) | 26% (3762) | 21% | 35% (269) | 38% (295) | 7.0% | 37% (91) | 26% (3467) |
| Body surface area (m ²) | 1.9 ± 0.2 | 1.9 ± 0.2 | 20% | 1.9 ± 0.2 | 1.9 ± 0.3 | 2.9% | 1.9 ± 0.3 | 1.9 ± 0.2 |
| Hypertension | 39% (395) | 60% (8555) | 43% | 42% (325) | 45% (351) | 6.8% | 29% (70) | 60% (8204) |
| Diabetes mellitus (Type I or II) | 15% (153) | 27% (3943) | 28% | 16% (121) | 16% (127) | 2.1% | 13% (32) | 28% (3816) |
| Peripheral vascular disease (History of aortoiliac, femoropopliteal, or carotid artery disease) | 11% (112) | 17% (2382) | 15% | 12% (92) | 12% (96) | 1.6% | 8% (20) | 17% (2286) |
| Cerebrovascular disease (History of stroke or transient ischemic attacks) | 11% (108) | 9% (1276) | 6% | 10% (79) | 12% (89) | 4.2% | 12% (29) | 9% (1187) |
| Atrial fibrillation | 17% (177) | 7% (962) | 41% | 17% (131) | 15% (119) | 4.2% | 19% (46) | 6% (843) |
| Left ventricular ejection fraction <40% | 24% (243) | 18% (2645) | 14% | 23% (177) | 19% (150) | 8.6% | 27% (66) | 18% (2495) |
| Unstable angina (within 30 d of surgery) | 13% (132) | 38% (5466) | 53% | 16% (122) | 15% (119) | 1.1% | 4% (10) | 39% (5347) |
| Recent myocardial infarction (within 30 d of surgery) | 2% (18) | 5% (709) | 15% | 2% (17) | 2% (14) | 2.8% | 0.4% (1) | 5% (695) |
| Recent cardiac catheterization (within 2 d of surgery) | 29% (293) | 7% (1018) | 79% | 25% (193) | 26% (199) | 1.8% | 41% (100) | 6% (819) |
| Active endocarditis | 8% (78) | 0.6% (80) | 72% | 6% (49) | 6% (43) | 3.3% | 12% (29) | 0.3% (37) |
| Preoperative estimated glomerular filtration rate (mL/min) | 82 ± 38 | 81 ± 32 | 2% | 79 ± 35 | 79 ± 36 | 0.5% | 91 ± 44 | 81 ± 32 |
| Preoperative hemoglobin concentration (g/dL) | 12.8 ± 2.1 | 13.5 ± 1.6 | 43% | 12.9 ± 2.0 | 12.9 ± 1.9 | 1.8% | 12.5 ± 2.2 | 13.6 ± 1.6 |
| Preoperative platelet count (×10 ⁹ /L) | 223 ± 78 | 233 ± 70 | 14% | 223 ± 77 | 223 ± 78 | 0.1% | 222 ± 82 | 233 ± 70 |
| Preoperative international normalized ratio of prothrombin time | 1.2 ± 0.4 | 1.1 ± 0.2 | 61% | 1.2 ± 0.4 | 1.2 ± 0.4 | 0.4% | 1.2 ± 0.4 | 1.1 ± 0.2 |
| Procedure | | | 121% | | | 4.2% | | |
| Isolated CABG | 10% (101) | 61% (8721) | | 13% (100) | 12% (94) | | 0.4% (1) | 64% (8627) |
| Any valve replacement or repair | 31% (312) | 22% (3104) | | 35% (268) | 33% (257) | | 18% (44) | 21% (2847) |
| Other procedures | 59% (604) | 18% (2533) | | 52% (404) | 55% (421) | | 82% (200) | 16% (2112) |
| Urgent surgery | 21% (214) | 7% (1074) | 49% | 20% (151) | 19% (148) | 1.0% | 26% (63) | 7% (926) |
| Redo sternotomy | 62% (626) | 5% (708) | 232% | 52% (402) | 53% (407) | 1.3% | 91% (224) | 2% (301) |
| CPB duration (min) | 143 ± 59 | 99 ± 36 | 118% | 134 ± 53 | 135 ± 59 | 1.4% | 172 ± 67 | 97 ± 33 |
| Deep hypothermic circulatory arrest | 12% (124) | 3% (447) | 48% | 12% (92) | 13% (97) | 2.0% | 13% (32) | 3% (350) |
| Large-volume RBC transfusion risk score ¹⁶ | 4.4 ± 1.6 | 1.4 ± 1.1 | 155% | 3.1 ± 1.5 | 3.1 ± 1.5 | 1.4% | 3.4 ± 1.6 | 1.5 ± 1.2 |
| Propensity score | 0.43 ± 0.3 | 0.04 ± 0.1 | 306% | 0.33 ± 0.26 | 0.33 ± 0.26 | 0.04% | 0.74 ± 0.14 | 0.02 ± 0.05 |
| Predicted risk for major adverse events ^a | 0.24 ± 0.15 | 0.16 ± 0.09 | 88% | 0.23 ± 0.14 | 0.24 ± 0.15 | 5.2% | 0.26 ± 0.16 | 0.15 ± 0.08 |

All data are presented as mean ± SD or percentages (n).

TA = tranexamic acid; SMD = Standard mean difference, which is the absolute mean difference divided by the pooled SD; CABG = coronary artery bypass graft surgery; CPB = cardiopulmonary bypass; RBC = red blood cell.

^a As calculated by the Toronto Risk Score prediction rule¹⁷; not included in the propensity-score calculations.

The final estimated propensity score model included 15 main-effects variables (with 41 degrees of freedom) and no interaction variables (*c*-index = 0.93) (Table 2). The model's most predictive variables, as measured by the Wald χ^2 , were the number of previous sternotomies, type of procedure, urgency, endocarditis, and surgeon

(Table 2). Of the 1017 patients who received aprotinin in the entire cohort, 772 (76%) were matched to similar patients who received tranexamic acid (Fig. 1). Covariate balance (standardized mean difference <10%) was achieved for all measured covariates (Table 1). Table 1 also shows the propensity scores and the predicted

Table 2. Propensity Score Model

| Variables (classification) | Degrees of freedom | Wald χ^2 | P |
|--|--------------------|---------------|---------|
| Age (continuous) | 1 | 6.9 | 0.009 |
| Cerebrovascular disease (categorical; yes or no) | 1 | 2.9 | 0.09 |
| Unstable angina (categorical; yes or no) | 1 | 3.6 | 0.06 |
| Endocarditis (categorical; none, remote, active, or active abscess) | 3 | 44.9 | <0.0001 |
| Preoperative dialysis (categorical; yes or no) | 1 | 3.9 | 0.05 |
| Preoperative intraaortic balloon pump (categorical; yes or no) | 1 | 1.8 | 0.2 |
| Preoperative hemoglobin concentration (continuous) | 1 | 3.4 | 0.07 |
| Surgeon (categorical; 13 surgeons) | 12 | 42.2 | <0.0001 |
| Procedure (categorical; aortocoronary bypass, valve, or other) | 2 | 73.1 | <0.0001 |
| Type of other procedures (categorical; 10 procedures such as heart transplant) | 9 | 22.9 | 0.006 |
| Urgency (categorical; elective, same hospitalization, urgent, emergent) | 3 | 51.7 | <0.0001 |
| Redo sternotomy (categorical; multiple previous, single previous, or no) | 2 | 618 | <0.0001 |
| CPB duration (continuous) | 1 | 13.7 | 0.0002 |
| Deep hypothermic circulatory arrest (categorical; ≤ 15 min, 16–29 min, ≥ 30 min) | 2 | 22 | <0.0001 |
| Large-volume RBC transfusion risk score (continuous) | 1 | 18.5 | <0.0001 |

CPB = cardiopulmonary bypass; RBC = red blood cell.

perioperative risk for major adverse events for the entire sample as well as for the matched and unmatched patients. As can be seen, balance was also achieved on these variables.

A suitable match could not be identified for 24% of patients who received aprotinin. Compared with matched aprotinin patients, these patients had markedly higher propensity scores (Table 1). This difference was primarily due to the high (91%) rate of previous sternotomies, with about half having undergone multiple previous sternotomies. Given the importance of this variable in estimating propensity scores (see above), this seems to have been the principal reason for not finding a suitable match for them.

Outcomes

The unadjusted observed adverse event rates were markedly higher in patients who received aprotinin than in those who received tranexamic acid (Table 3). After propensity score matching, however, aprotinin was only associated with increased risk of acute kidney injury (odds ratio 1.5; 95% confidence interval [CI] 1.1–2.1) (Table 3).

The cubic spline function curves of the predicted risk for adverse events versus observed rates of mortality, acute kidney injury, and massive blood loss in the matched group are shown in Figure 2a–c, respectively. As can be seen, there was an important interaction between patients' risk status and the relative risk-benefit profile of the drugs. For mortality and massive blood loss, the risk-benefit profile of aprotinin changed from unfavorable to favorable when the predicted risk for adverse events was approximately 0.3. This risk level corresponded to approximately the 75th percentile in the matched group (and the 90th percentile in the entire study population). A similar pattern was observed for acute kidney injury (as well as for other measured adverse events, the results of which are not shown) but at a markedly higher

Table 3. Outcomes

| Outcomes ^a | Entire sample | | | Matched patients | | |
|---|----------------------|-----------------|---------|---------------------|--------------|-------|
| | Aprotinin (n = 1017) | TA (n = 14,358) | P | Aprotinin (n = 772) | TA (n = 772) | P* |
| Death | 9% (87) | 2% (247) | <0.0001 | 7.0% (54) | 7.4% (57) | 0.8 |
| Acute kidney injury | 15% (149) | 4% (564) | <0.0001 | 13.5% (104) | 9.2% (71) | 0.009 |
| Massive blood loss | 25% (256) | 8% (1077) | <0.0001 | 21.4% (165) | 21.2% (164) | 0.9 |
| Other measured outcomes | | | | | | |
| Received at least 1 RBC unit | 81% (826) | 61% (8816) | <0.0001 | 78% (604) | 79% (609) | 0.8 |
| Received platelets | 60% (613) | 19% (2771) | <0.0001 | 56% (429) | 53% (410) | 0.3 |
| Received fresh frozen plasma | 68% (696) | 29% (4226) | <0.0001 | 65% (498) | 65% (501) | 0.9 |
| Acute kidney failure requiring dialysis support | 7.4% (75) | 1.3% (187) | <0.0001 | 5.6% (43) | 3.6% (28) | 0.07 |
| Myocardial infarction | 3% (26) | 2% (275) | 0.1 | 3.0% (23) | 2.3% (18) | 0.4 |
| Stroke | 4% (38) | 1% (189) | <0.0001 | 3.6% (28) | 2.3% (18) | 0.1 |
| Serious infection | 6% (65) | 2% (310) | <0.0001 | 5.7% (44) | 4.7% (36) | 0.4 |

TA = tranexamic acid; RBC = red blood cell.

^a See text for definitions.

* Conditional logistic regression used.

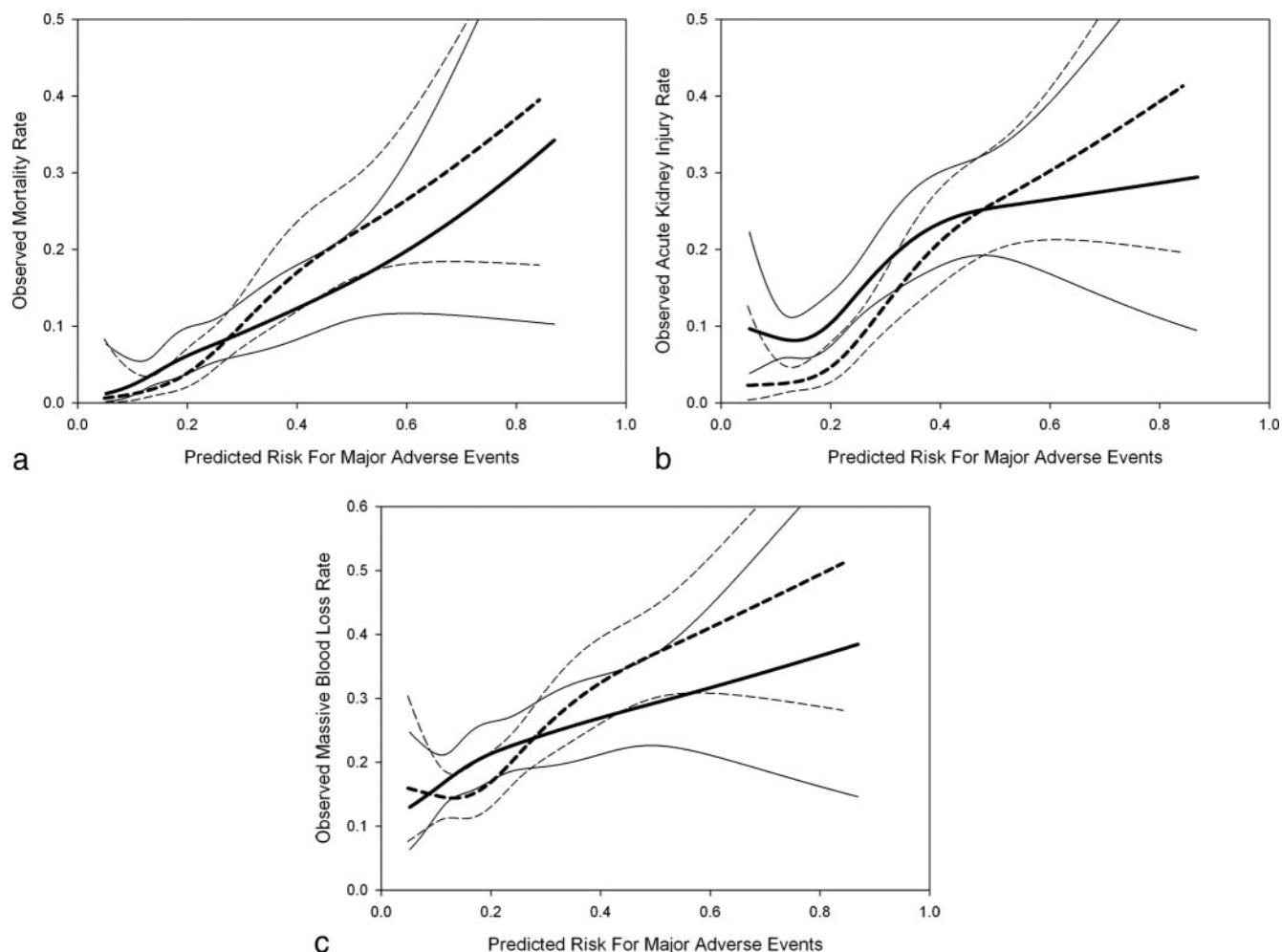


Figure 2. Relationship between patients' predicted adverse event rates, as calculated using the Toronto Risk Score regression formula, and the rates of mortality (a), acute kidney injury (b), and massive blood loss (c) in the matched group. These relationships were modeled using restricted cubic spline functions. Solid lines represent patients who received aprotinin, and dashed lines represent those who received tranexamic acid. Faded lines are the 95% confidence intervals of the relationships.

predicted adverse event rate of approximately 0.5 (which corresponded to the 95th percentile in the matched set and 99th percentile in the entire study population).

Using the predicted risk for major adverse events of 0.3 as the threshold for categorizing patients as high risk, the odds ratio for mortality associated with aprotinin use in the matched group was 0.6 (95% CI 0.3–1.0; $P = 0.05$) in high-risk patients and 1.5 (95% CI 0.9–2.7; $P = 0.1$) in the remaining patients (Fig. 3a; Breslow-Day test, $P = 0.01$), the odds ratio for acute kidney injury was 1.1 (95% CI 0.7–1.7; $P = 0.8$) in high-risk patients and 2.2 (95% CI 1.4–3.5; $P = 0.0006$) in the remaining patients (Fig. 3b; Breslow-Day test, $P = 0.03$), and the odds ratio for massive blood loss was 0.7 (95% CI 0.4–1.04; $P = 0.07$) in high-risk patients and 1.2 (95% CI 0.9–1.7; $P = 0.2$) in the remaining patients (Fig. 3c; Breslow-Day test, $P = 0.02$).

Matched high-risk patients had the following characteristics: 25% had unstable angina, 41% had left

ventricular dysfunction, 25% had peripheral vascular disease, 45% had elevated baseline creatinine concentrations, 54% had 1 or more previous sternotomies, 46% underwent urgent surgery, and 81% underwent complex surgical procedures (i.e., procedures other than isolated CABG or single valve) with an average CPB duration of 143 (SD \pm 57) min.

DISCUSSION

Despite the widespread, long-term use of the anti-fibrinolytic drugs aprotinin and tranexamic acid in cardiac surgery, little is known about their comparative risk-benefit profile, particularly in the setting of complex, high-risk surgeries in which, because of high excessive blood loss and complication rates, differences in their potency and side effect profile can have important prognostic implications.

In this study, we compared the risk-benefit profile of aprotinin and tranexamic acid in cardiac surgery across a wide spectrum of risk, ranging from simple,

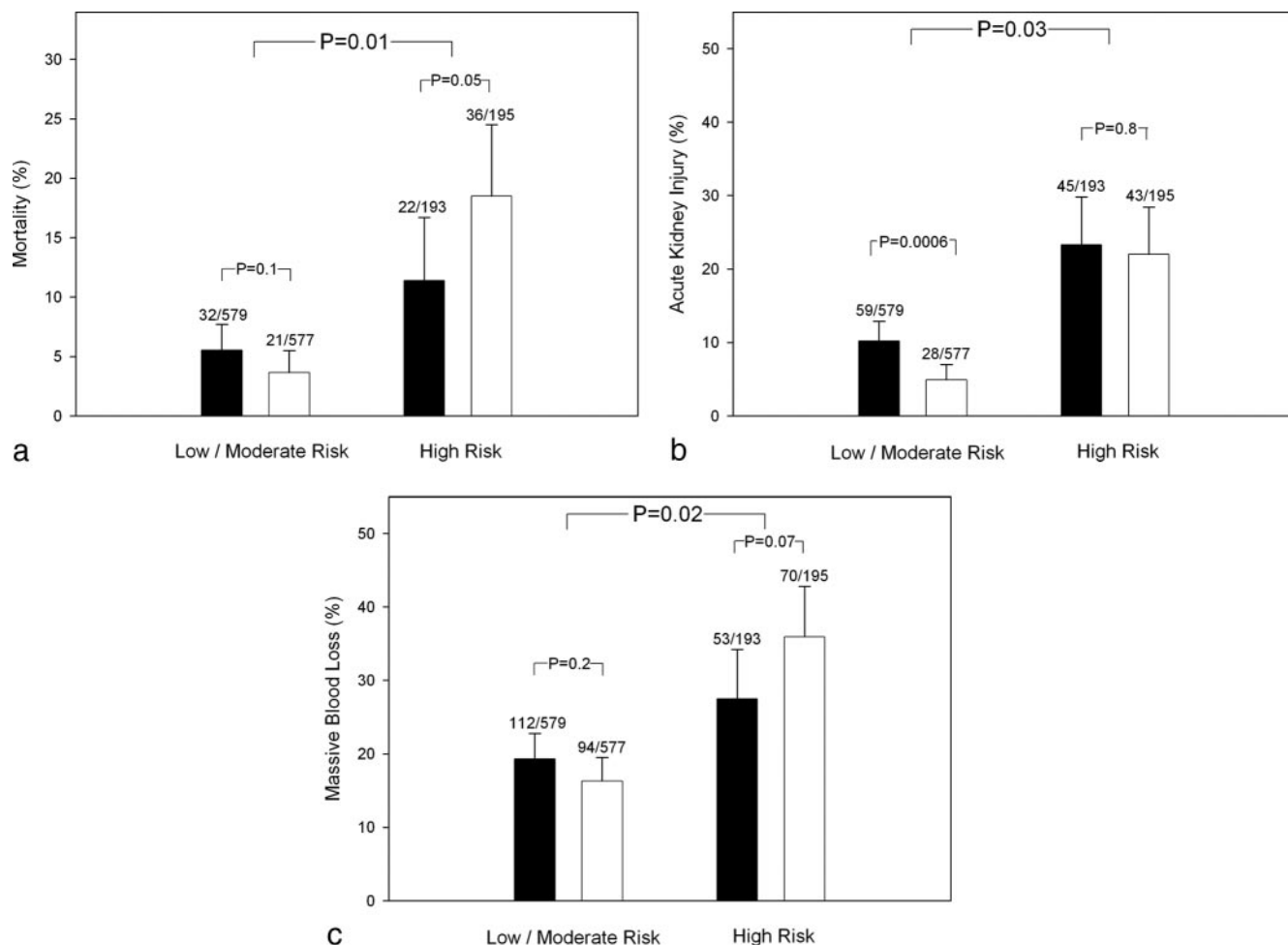


Figure 3. The differential effects of aprotinin versus tranexamic acid on mortality (a), acute kidney injury (b), and massive blood loss (c) relative to patients' risk status in the matched group. Patients whose predicted risk for major adverse events was >0.3 are classified as high risk. Patients who received aprotinin are represented in black, and those who received tranexamic acid in white. Bars are the SD. The χ^2 test was used to compare the rates within each risk category. The Breslow-Day test was used to determine whether drug effects were significantly different between the risk categories.

low-risk surgeries to complex, high-risk surgeries. When we matched patients who received aprotinin to similar patients who received tranexamic acid based on their propensity scores and compared their outcomes at the group level, we found that aprotinin use was associated with increased risk of acute kidney injury but not with any of the other measured adverse outcomes. When we then examined the influence of patients' risk status on measured outcomes, however, we found that high-risk patients had a significantly different response to aprotinin than low- to moderate-risk patients. Specifically, we found that aprotinin tended to be associated with less massive blood loss and lower adverse event rates in patients whose risk status placed them in the top 25th percentile of the matched group (which corresponded to the top 10th percentile of our institution's cardiac surgery population), but it tended to be associated with higher adverse event rates in lower-risk patients.

We measured patients' risk status by a risk score that was developed and validated at our institution

that incorporated several patient- and surgery-related variables. Given that the principal determinants of high risk were the urgency and complexity of surgery, however, our estimates should be externally generalizable. Our findings are also physiologically plausible, because it is in these types of cases that patients frequently develop profound coagulopathy, systemic inflammatory response syndrome, or both.⁷ It is therefore in these types of cases that, compared with tranexamic acid, aprotinin's greater hemostatic and antiinflammatory potency should outweigh its greater proclivity for hypercoagulability, renal dysfunction, and hypersensitivity.²⁴

The clinical implication of our findings is that aprotinin may be the antifibrinolytic of choice and should therefore remain available for clinical use in patients undergoing high-risk cardiac surgery. These are the patients who are undergoing emergency, complex procedures that require prolonged CPB support, and they constitute approximately 10% of the general cardiac surgery population. This finding

is highly relevant because neither the United States Food and Drug Administration nor Health Canada has made a final determination on the status of aprotinin.

Our findings are consistent with most pertinent data. As in our study, a recent comprehensive meta-analytical analysis of randomized clinical trials that were published before the BART trial found that aprotinin is associated with increased risk of acute kidney injury but not with any other adverse events.²⁵ On the other hand, several recent observational studies,^{8–10} as well as the randomized BART trial,¹¹ have found aprotinin to also be associated with higher risks of other adverse events and mortality. For the most part, however, these studies included CABG surgeries, and their analysis was therefore limited to low- to moderate-risk cases. Even in the BART trial, where the objective was to assess aprotinin in high-risk cases, patients undergoing emergency or most types of complex surgery were excluded.¹¹ As a result, the study's sample consisted primarily of low- to moderate-risk cases. When we calculated the risk status of the 144 patients that our institution contributed to the BART trial with the Toronto Risk Score, we found that their median predicted perioperative risk for major adverse events was 0.16 (25th and 75th percentile 0.12; 0.23), which would have placed them in the low- to moderate-risk category of our matched group. It would be surprising if the risk profiles of patients from other centers differed substantially from ours. It seems, therefore, that the results of the BART trial may not be applicable to high-risk cases.

Our study has several limitations. First, because patient allocation was not randomly determined and patients could only be matched based on measured covariates, there may be between-group differences in unmeasured confounders. Because aprotinin was preferentially used in higher-risk cases, we would anticipate unmeasured confounders to bias our results against aprotinin. This, therefore, cannot explain why we found aprotinin to be associated with improved outcomes in high-risk cases. Another possible source of bias relates to changes in clinical practice or case mix that may have occurred during the study period. Although we deliberately did not control for year of surgery to increase the number of matches, we did control for multiple measures of comorbidity, surgical complexity, and the individual surgeon. Moreover, clinical practice at our institution did not undergo major changes during the study period, and the measured outcome rates were relatively constant during the entire study period (results not shown). Thus, the unmeasured temporal influences on our results should be small. Another limitation of this study is that it lacked a placebo control group and, therefore, provides no information on the overall risks and benefits of using antifibrinolytic drugs in cardiac surgery. Finally, given that this was an observational

study, we can only comment on associations and cannot prove causation. Thus, an adequately powered, randomized, comparative clinical trial aimed at patients undergoing high-risk cardiac surgery is needed to verify our findings. The high adverse event rates in this group of patients makes the conduct of such a study quite feasible.

In summary, we conducted a single-center cohort study in which we compared the outcomes of 772 cardiac surgical patients who received aprotinin with 772 propensity score-matched patients who received tranexamic acid from 2000 to 2008. As in previous studies, we found that aprotinin was associated with increased overall risk of acute kidney injury. We also found, however, that the effects of aprotinin were significantly influenced by the patients' risk status, such that it tended to be associated with lower massive blood loss and adverse event rates in high-risk patients, but not in low- to moderate-risk patients. Thus, our findings suggest that the use of aprotinin may be warranted in patients whose risk status, as determined by their comorbidities, surgical acuity, and complexity, places them at approximately the top 10th percentile of the cardiac surgery population. Our findings need to be verified by randomized controlled trials in high-risk cases.

APPENDIX. The Toronto Risk Score¹⁷ for Predicting Major Adverse Events Following Cardiac Surgery

| Variable | Regression coefficient | Weight |
|--|------------------------|--------|
| Age 65–74 yr | 0.074 | 1 |
| Age ≥75 yr | 0.226 | 2 |
| Female sex | 0.404 | 2 |
| Left ventricle ejection fraction 20%–40% | –0.068 | 2 |
| Left ventricle ejection fraction <20% | 0.515 | 3 |
| Urgent case | –0.312 | 1 |
| Emergent case | 0.846 | 6 |
| Myocardial infarction within 30 d of surgery | 0.353 | 1 |
| Redo coronary artery bypass surgery | 1.106 | 4 |
| Triple vessel disease | 0.286 | 1 |
| Left main disease | 0.312 | 1 |
| Congestive heart failure | 0.326 | 2 |
| Preoperative creatinine >150 μmol/L | 0.718 | 2 |
| Diabetes (Types I or II) | 0.205 | 1 |
| Peripheral vascular disease | 0.296 | 1 |
| Hypertension | 0.142 | 1 |
| Complex valve surgery (>1 valve or 1 valve plus additional procedures) | 0.295 | 2 |
| Other pathology requiring surgical correction | 0.617 | 2 |
| Constant | –2.595 | — |

The predicted probability of adverse events is calculated using the formula: Probability = $\Sigma e^{\beta} / (1 + \Sigma e^{\beta})$, where e is the exponent and β is the regression coefficient.

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Plasmapheresis and Heparin Reexposure as a Management Strategy for Cardiac Surgical Patients with Heparin-Induced Thrombocytopenia

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BACKGROUND: Heparin-induced thrombocytopenia (HIT) complicates the management of patients presenting for cardiac surgery, because high-dose heparin anticoagulation for cardiopulmonary bypass is contraindicated in these patients. Alternative anticoagulants are available, but there are concerns about dosing, efficacy, monitoring, thrombosis, and hemorrhage.

METHODS: A retrospective chart review between November 2004 and March 2008 retrieved perioperative clinical and laboratory data for 11 adult cardiac surgical patients with a preoperative history of HIT and a current positive antiheparin/platelet factor 4 (anti-HPF4) antibody titer, who were managed with plasmapheresis and heparin anticoagulation.

RESULTS: The median (interquartile range) preoperative anti-HPF4 antibody titer was 0.8 (0.7–2.2). Three of the 11 patients (27%) died of causes unrelated to HIT and 1 of these patients (9%) developed an ischemic foot, in the setting of cardiogenic shock, not thought to be HIT-related. A single plasmapheresis treatment reduced titers by 50%–84%, and 6 patients had negative titers after treatment; none of the 3 patients with reduced titers developed clinical HIT.

CONCLUSIONS: This case series describes an alternative management strategy using intraoperative plasmapheresis for patients presenting for cardiac surgery with acute or subacute HIT. Reducing antibody load can potentially decrease the thrombotic risk associated with high anti-HPF4 titers and decrease the urgency to initiate postoperative anticoagulation in this patient group at high risk of postoperative bleeding.

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Heparin-induced thrombocytopenia (HIT) complicates the management of patients presenting for cardiac surgery. Current standard practice for anticoagulation during the extracorporeal circulation of cardiopulmonary bypass (CPB) relies on high-dose heparin with rapid reversal of the anticoagulant effect using protamine sulfate. Although nonheparin, alternative anticoagulants such as recombinant hirudin, argatroban, danaparoid, fondaparinux, and ancrod have been available for use in patients at risk of HIT or HIT complicated by thrombosis (HITT),¹ these drugs are seldom used in the surgical setting because of concerns about efficacy, safety, and lack of reversal drugs. For example, danaparoid and fondaparinux have half-lives of more than 18 h, and ancrod is no longer approved or available. Argatroban and recombinant

hirudin (Lepirudin/Refludan, Bayer Healthcare, Montville, NJ) have been associated with excessive hemorrhage, and argatroban (GlaxoSmithKline, Durham, NC) with adverse thrombotic outcomes.^{2–6}

Bivalirudin (Angiomax®, The Medicines Company, Parsippany, NJ), a direct thrombin inhibitor, may prove to be an acceptable anticoagulant substitute for CPB, based on several prospective randomized studies.^{7–9} Despite this extensive published experience in CPB, bivalirudin is used only as an alternative drug for HIT patients requiring cardiac surgery because of concerns over monitoring bivalirudin therapy during CPB. Although the ecarin clotting time is the preferred monitoring test for bivalirudin, this test is currently not available in the United States.^{10,11} The manufacturer recommends using the activated clotting time (ACT), which is used for monitoring heparin therapy, but the ACT does not reliably predict the anticoagulant effects of bivalirudin at larger doses.^{12,13} Also, there are concerns about severe bleeding when using bivalirudin anticoagulation monitored with the ACT,¹⁴ especially because there is no available reversal drug. Limitations to bivalirudin include visible clotting that has been reported in stagnant areas of the extracorporeal circuit during bivalirudin anticoagulation, leading

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to concerns about the potential for microembolization and/or frank thrombosis.^{9,15}

These concerns about the safety of bivalirudin have led us and others to adopt a variety of strategies for managing complex cardiac patients with HIT in need of CPB.^{16,17} At our institution, when possible, surgery is delayed until antibodies are cleared from the circulation, because antiheparin/platelet factor 4 (anti-HPF4) antibodies are transient¹⁸ and reports suggest that reexposing patients to heparin is safe in this setting.¹⁹ For patients whose surgery cannot be delayed, we have also reported on the safety of limiting heparin exposure during the perioperative period and exposing patients only during CPB.¹⁶ Others have advocated the utility of testing the functional effects of anti-HPF4 and limiting surgery to only those patients whose anti-HPF4 does not activate platelets.¹⁷ However, these latter 2 strategies for managing patients with acute or subacute HIT continue to place patients at risk for intraoperative or postoperative thrombotic outcomes as anti-HPF4 either remains in circulation or increases after heparin exposure. Circulating anti-HPF4 can activate platelets even in the absence of heparin^{20,21} and can also activate endothelial cells and leukocytes.²² Patients with acute coronary syndromes and positive HPF4 antibodies, even in the absence of thrombocytopenia, have an increased incidence of death or myocardial infarction at 30 days and beyond compared with seronegative patients.^{23,24} Recent studies also indicate that the risk of thrombosis and adverse events with anti-HPF4 is correlated with antibody titer.²⁴

Plasmapheresis to clear HIT antibodies has been reported to stabilize platelet count and normalize platelet aggregation in patients with HIT and even alleviate HIT after heparin exposure in the operating room.^{25–27} Because plasmapheresis can reduce levels of circulating antibodies in a variety of disease settings,^{28,29} we have used plasmapheresis in the operating room to reduce circulating anti-HPF4 levels in patients with a history of HIT undergoing CPB with heparin. This strategy was designed to decrease antibody titers and minimizes both the intraoperative risk of heparin exposure and potential risk of thrombosis after the procedure. This report describes 11 patients with a history of HIT and a positive anti-HPF4 enzyme-linked immunosorbent assay (ELISA) managed with intraoperative plasmapheresis and their postoperative outcomes.

METHODS

Study Design

After obtaining IRB approval, we performed a retrospective chart review of all patients receiving plasmapheresis in the operating room after July 2004, when we first performed this procedure for the indication of HIT, with follow-up extending to June 2008. Plasmapheresis was performed using a COBE® Spectra Apheresis System (CaridianBCT, Lakewood, CO)

after induction of general anesthesia with endotracheal intubation, initiation of intermittent positive pressure ventilation, invasive hemodynamic monitoring (radial arterial pressure, central venous pressure, pulmonary artery pressure, and thermodilution cardiac output), and transesophageal echocardiographic monitoring of cardiac function. Plasma exchange was performed with fresh-frozen plasma replacement using a 1.3 plasma volume exchange (approximately 2000–3000 mL based on patient's height, weight, gender, and hematocrit). The Nadler algorithm³⁰ was used to calculate blood volume; blood volume was multiplied by 1-hematocrit to calculate plasma volume.

The timing of plasmapheresis was dependent on the hemodynamic stability of the patient. Ideally, it was performed before heparinization, but if necessary (400 U/kg), heparin was given, CPB initiated to stabilize the patient, and plasmapheresis performed during CPB as previously described.²⁵ Because heparin is removed during plasmapheresis, additional heparin was infused during the exchange based on the following estimation. Assuming a hematocrit of 0.25, we replaced heparin lost during plasmapheresis as calculated by 4 U/mL of plasma removed administered as a 4000-U bolus after every liter removed with any remainder at completion of the treatment.

Postoperatively, bivalirudin anticoagulation with an activated partial thromboplastin time target of 50–60 s was planned if a platelet count pattern was suggestive of HIT,³¹ postoperative bleeding had ceased, and thoracostomy tubes had been removed. Patients were also transitioned to oral coumadin to manage anticoagulation for mechanical heart valves, ventricular assist devices (VADs), and/or HIT.

Data Collection

Patient characteristics, perioperative platelet count profiles, anti-HPF4 levels, thrombotic complications, and survival status up to 1 yr were recorded. HIT was diagnosed based on appropriate timing of platelet count decrease (30%–50% decrease from baseline platelet count decrease) and/or thrombosis in the setting of anti-HPF4 antibodies and recorded in the patient's chart by a hematologist either at Duke University or at a referring hospital. The anti-HPF4 antibody titers are described as an optical density (OD) based on the colorimetric ELISA measuring polyclonal antibodies to HPF4 (immunoglobulin [Ig]G, A, M ELISA, GTI, Wahkesha, WI). A positive result is defined by the manufacturer as OD >0.4. Confirmatory testing with excess heparin was reported when available, with >50% decrease in the OD with excess heparin as confirmatory of HPF4-specific antibodies.³² Descriptive data are presented as a median with the interquartile range or as a range of values.

RESULTS

During the study period, the indication for intraoperative plasmapheresis was clearance of panel reactive

Table 1. Patient Characteristics

| Case no. | Diagnosis | Age at operation | Procedure | Postoperative anticoagulation | Indication for anticoagulation | Thrombotic complications | Death |
|----------|---------------------|------------------|-----------------------------|-------------------------------|--------------------------------|----------------------------|-----------------------|
| 1 | NICM/cardiac arrest | 27 | BiVAD | Bivalirudin, coumadin | VAD | Nil | No |
| 2 | NICM | 69 | Replace malfunctioning LVAD | None | | Nil | 6 mo postsurgery |
| 3 | NICM | 56 | OHT | Bivalirudin, coumadin | IABP/thrombosis | Left foot loss due to IABP | 3 mo postsurgery |
| 4 | CAD, AS, MS | 41 | CABG × 4, AVR, MVR | Bivalirudin, coumadin | Mechanical valve | Nil | No |
| 5 | ICM, AS | 49 | OHT | None | | Nil | No |
| 6 | CAD, AS | 74 | Emergent AVR | Bivalirudin, coumadin | Mechanical valve | Nil | No |
| 7 | Viral myocarditis | 23 | Explant LVAD | None | | Nil | No |
| 8 | ICM | 50 | Explant LVAD/OHT | None | | Nil | No |
| 9 | Hemochromatosis | 36 | Explant LVAD/OHT, OLT | None | | Nil | Over 1 yr postsurgery |
| 10 | NICM | 50 | Explant LVAD/OHT | None | | Nil | No |
| 11 | NICM | 58 | Explant LVAD/OHT | None | | Nil | No |

NICM = nonischemic cardiomyopathy; BiVAD = biventricular assist device; VAD = ventricular assist device; LVAD = left ventricular assist device; OHT = orthotopic heart transplant; CAD = coronary artery disease; AS = aortic stenosis; MS = mitral stenosis; ABS = aortocoronary bypass surgery; AVR = aortic valve replacement; MVR = mitral valve replacement; ICM = ischemic cardiomyopathy; OLT = orthotopic liver transplant.

antibodies (anti-human leukocyte antigen panel, One Lambda, Canoga Park, CA) before implantation of cardiac or pulmonary allografts ($n = 33$), clearance of anti-HPF4 antibodies ($n = 9$), or both ($n = 2$); the latter 2 categories ($n = 11$) were included in this report.

Of the 11 patients, 9 had a preoperative diagnosis of HIT within 2 wk of the operation, and 2 patients had a history of HIT and a positive HPF4 ELISA (OD >0.4) within 2 mo of the procedure. The latter 2 received plasmapheresis for the indication of high panel reactive antibody titers (these antibodies confer risk of acute, humoral allograft rejection) in addition to a history of HIT and a positive HPF4 ELISA. None of the patients had a positive heparin-induced platelet aggregation assay, using platelets from 3 separate donors.

Table 1 presents the descriptive data of the patient series. Seven of 11 (64%) were re sternotomies with most of these patients having had a VAD inserted for cardiogenic shock or end-stage cardiomyopathy. The immediate perioperative courses of these patients were unremarkable for this patient group and involved the need to manage low cardiac output syndrome, right ventricular dysfunction, and postoperative hemorrhage.

One patient developed an ischemic foot. This patient required intraaortic balloon pump support for a profound low cardiac output state resulting from pericardial tamponade and postoperative hemorrhage that necessitated cardiopulmonary resuscitation and emergency re sternotomy. The initial plasmapheresis treatment in this patient had reduced the anti-HPF4 antibody titer from an OD of 0.86 to 0.3, and she underwent a second treatment for possible acute, humoral rejection. The OD after the second treatment was 0.44 in the setting of an increasing platelet count and improving cardiac function, so a third treatment was not undertaken. The thrombotic episode in this

patient was not believed to be due to HIT based on the observations of a systemic hemorrhagic state, low OD (0.3) at time of thrombosis, and the presence of an intraaortic balloon pump in the affected leg. The patient had no further thrombotic episodes but subsequently succumbed to vancomycin-resistant enterococcal mediastinitis 3 mo after orthotopic heart transplantation.

Three of the 11 patients (27%) died of causes unrelated to HIT. In addition to the patient described above, a second patient died from a hemorrhagic stroke 6 mo after replacement of a failing Heartmate XVE (Thoratec, Pleasanton, CA) with another Heartmate XVE left VAD. Aspirin was used, as recommended, and no other anticoagulants were being used at the time of the stroke. The platelet count was stable ($97\text{--}158 \times 10^9/\text{L}$) in the month preceding this stroke, and, therefore, death was not thought to be HIT related. A third patient died from acute, upper gastrointestinal hemorrhage, in the setting of methicillin-resistant *Staphylococcus aureus* sepsis, 14 mo after a combined orthotopic heart and liver transplant. The platelet count was low ($30\text{--}70 \times 10^9/\text{L}$) in the weeks preceding death consistent with sepsis, and a repeat anti-HPF4 obtained at readmission was negative with an OD of 0.24. Platelet transfusions were given to treat thrombocytopenia in the setting of bleeding but the platelet count was rarely higher than $100 \times 10^9/\text{L}$.

The median preoperative antibody titer was 0.8 (0.7–2.2) and a single plasmapheresis treatment reduced titers by 50%–84%. After treatment, 6 of the 9 patients with available postoperative ELISA results had normal HPF4 levels as shown in Figure 1. The other 3 patients initially had particularly high titers that were reduced by 48%, 68%, and 78%, respectively (OD reduced from 2.5 to 1.3, 2.7 to 0.84, and 2.2 to 0.5 after plasmapheresis). In these 3 patients, platelet

Figure 1. Antiheparin/platelet factor 4 (PF4) (heparin-induced thrombocytopenia [HIT] antibody) enzyme-linked immunosorbent assay optical density before and after plasmapheresis in the operating room. The upper limit of normal in our laboratory is an optical density of 0.4.

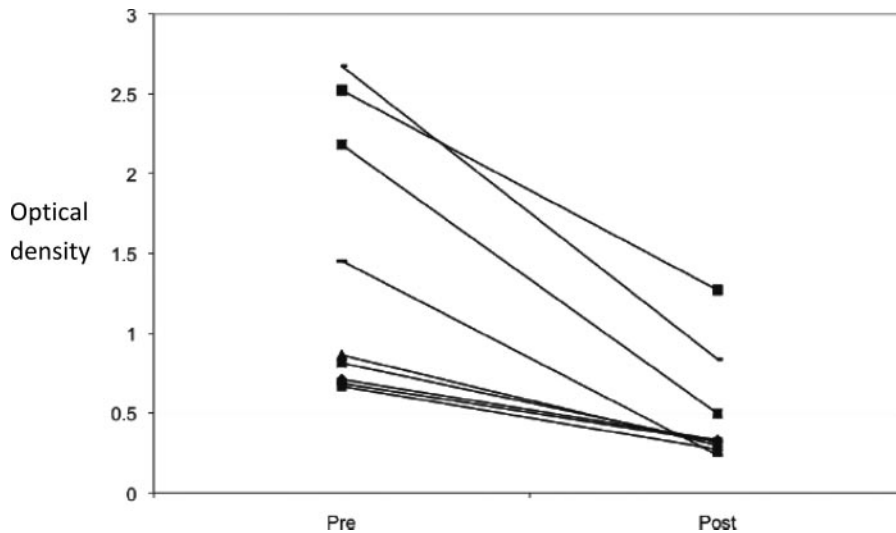
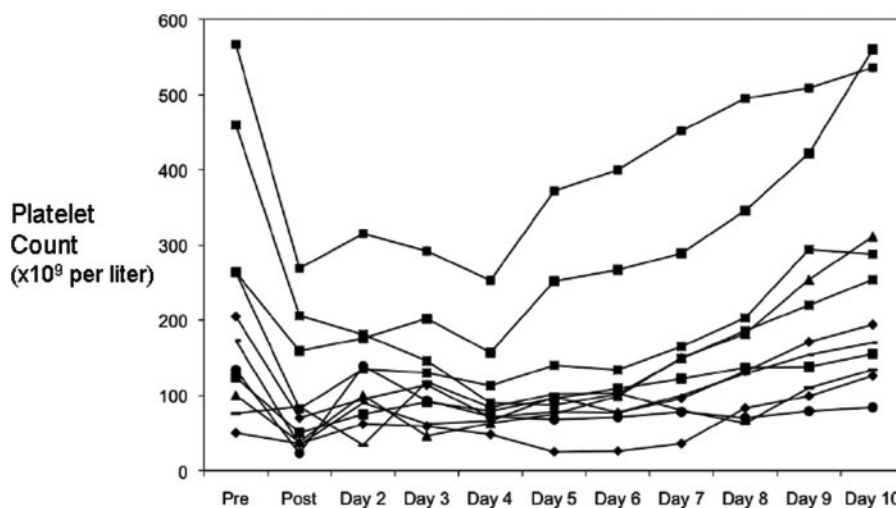


Figure 2. Perioperative platelet count profile from the day of surgery to the 10th postoperative day.



counts recovered to normal after surgery and were stable, so further plasmapheresis treatments were not thought to be clinically indicated. The decision to continue plasmapheresis treatments was based on suspicion of HIT (platelet count recovery pattern³³ and/or evidence of thrombosis) or whether concurrent, high panel reactive antibody titers presented a continued clinical risk for allograft rejection. Repeat anti-HPF4 antibody ELISA testing was performed postoperatively, but because they were performed by batch analysis, the results were rarely available to guide the clinical decisions described above.

No patients demonstrated the triphasic platelet count pattern typical of HIT occurring after CPB.^{31,33} Platelet counts typically reached a nadir on the day of surgery and steadily recovered during the first postoperative week (as shown in Fig. 2). Anticoagulation was not required to treat HIT in any of this series of patients. Seven of 11 patients (64%) were not electively anticoagulated after the procedure. The remaining 4 patients were bridged to coumadin with IV bivalirudin because of placement of mechanical heart valves or VADs.

DISCUSSION

We present a series of patients presenting for urgent, complex cardiac surgery with a recent diagnosis of HIT and a positive anti-HPF4 antibody screen. Patients were successfully managed with a strategy of intraoperative plasmapheresis, heparin reexposure during surgery, and daily monitoring of platelet counts.

It has been shown that patients with a history of HIT and a negative HPF4 antibody screen at the time of surgery can safely be given heparin.¹⁹ However, the management of patients with circulating anti-HPF4 remains problematic. In most of our patients (9 of 11), the platelet count had recovered between the time of HIT diagnosis and heparin reexposure, but all patients had circulating antibodies detectable by ELISA. None of the patients had HIT at the time of surgery or positive platelet aggregation assays, but several patients had high titers of circulating antibodies, which placed them at risk for intraoperative or postoperative thrombotic complications.

It is possible that a more aggressive plasmapheresis strategy could have been implemented in our cohort,

previously described for treating HIT,^{25–27} because not all patients converted to a negative titer. However, antibody titers were significantly reduced in all our patients (50%–84%), which could theoretically decrease the risk of thrombosis in these patients.^{24,34} Repeated treatments, to achieve a negative titer, were not pursued in our patient cohort; all of our patients had stable platelet counts postoperatively and had no evidence of thrombosis. Because patients had stable platelet counts, we did not pursue postoperative plasmapheresis because of concerns about hemodynamic instability and exposure to additional blood products.

Conversely, it is possible that our treatment strategy may have been too aggressive. Whether decreasing anti-HPF4 from low values to near-normal levels confers additional benefit remains to be determined. Current American College of Chest Physicians guidelines recommend that patients with a history of HIT should not be reexposed to heparin until antibody levels are undetectable. For this reason, we elected to pursue a conservative approach reducing antibody levels to the lowest level achievable rather than subjecting patients to an unknown risk of disease exacerbation.

Although it would be optimal to select patients for plasmapheresis based on results of functional assays, this approach is often not practical. Functional testing for HIT antibodies is not standardized and is technically challenging. Only a few regional laboratories in the United States perform the serotonin release assay, which is widely regarded as the functional assay with the highest sensitivity and specificity.¹ The platelet aggregation assay, which we use at our institution, is far less sensitive than the serotonin release assay³⁵ and a negative result can therefore be potentially misleading because of the low sensitivity of the assay. Alternatively, we could have used a prespecified OD value for treating patients only with high anti-HPF4 titers, which are more likely to promote platelet activation³⁶ and cause thrombosis.³⁴ However, there is no universally agreed “cutoff” for defining high-titer antibodies; some studies indicate that an OD >1.0 confers a heightened risk of thrombosis, whereas others suggest that risk is not significantly increased unless antibodies capable of platelet activation are detected, which usually occurs at OD >1.4.³⁶ Given this uncertainty and the recognition that some patients with “lower” titers (OD 0.5–0.8) can also manifest thrombosis,^{33–35} we elected to make treatment decisions based on positive ELISA results without regard to a specific cutoff value.

In the future, introduction of specific IgG assays to routine practice may improve the specificity of antibody testing, although a positive titer in a polyclonal assay could still be due to IgG antibodies and associated with platelet-activating antibodies.³⁵

We recognize that our report has important limitations: the data are retrospective; it is a small series with no randomization of therapy or comparison to treatment strategies, and the report is not powered or

designed to demonstrate risks or benefits of the plasmapheresis procedure compared with heparin anticoagulation alone or a heparin alternative; and the small size of our study population also precludes any meaningful conclusions about safety or efficacy. Risks of plasmapheresis, including hemodynamic instability, hypocalcemia, and exposure to a large volume of allogeneic plasma, were thought to outweigh the potential hazards of intraoperative thrombosis from HIT and/or exacerbating the anti-HPF4 response with further exposure. We also thought that these risks associated with plasmapheresis were mitigated by performing the procedure in the operating room with the benefit of invasive hemodynamic monitoring, repeated ionized calcium measurements, and intermittent positive pressure ventilation with the option of CPB for circulatory support.

Despite these limitations, our report provides important background for future clinical trials of plasmapheresis for the management of anti-HPF4 seropositive patients in need of cardiac surgery. Although our numbers were small, we found no definite evidence of postoperative HIT or HITT and no hemodynamic instability with plasmapheresis. By decreasing antibody titers, we were able to circumvent the need for postoperative anticoagulation in 7 of the 11 patients (64%). Having the option to reasonably avoid anticoagulation in the postoperative period is desirable, because bleeding may further complicate management in this high-risk population.

In summary, we describe the use of intraoperative plasmapheresis and heparin reexposure in patients presenting for complex cardiac surgery with a history of HIT and positive anti-HPF4 antibodies who were believed to be unsuitable candidates for nonheparin anticoagulants. Intentional heparin reexposure has been described in the setting of HIT,^{1,16,17,37,38} but this case series describes an extension of this strategy with intraoperative plasmapheresis to reduce antibody titers and decrease the urgency to initiate postoperative anticoagulation in this patient group at high risk of postoperative bleeding.

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Native Aortic Root Endocarditis with Invasion of the Right Outflow Tract

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Consent for publication was obtained from the patient's family. A 45-yr-old diabetic man presented with fever and pleuritic chest pain. Blood cultures obtained yielded methicillin-sensitive *Staphylococcus aureus*. A transthoracic echocardiogram showed a large vegetation involving the right coronary leaflet of the aortic valve consistent with endocarditis. Intravenous antibiotic therapy was initiated. A transesophageal echocardiogram (TEE), performed 48 h later, revealed new severe aortic regurgitation, a large aortic root abscess, and a mass in the right ventricular outflow tract (RVOT). The patient was scheduled for urgent surgical intervention the next day.

After induction of anesthesia, TEE examination revealed a small pericardial effusion without signs of tamponade. Starting at the midesophageal short-axis aortic view, the aortic root was interrogated for abscess extension by varying the angulation of the multiplane transducer. A vegetation was present on a thickened right coronary cusp of the aortic valve. Periannular abscess formation extending from the right coronary orifice anteriorly to the left coronary orifice laterally was noted (Fig. 1) (Video clip 1, see Supplemental Digital Content 1, <http://links.lww.com/AA/A38>. Midesophageal aortic valve short-axis: aortic root abscess is shown

with thickening and increased echolucency of both areas of left [arrow 1] and right [arrow 2] proximal coronary arteries. Both bases of the right and left coronary leaflets are thickened; thickening of the free edge of the right coronary cusp with attached strands is noted. A small pericardial effusion is also present [arrow 3].). The proximal right and left main coronary arteries were surrounded by the abscess. Abscess extension longitudinally toward the muscular interventricular septum and the right sinus of Valsalva was noted by rotating the probe rightward from the midesophageal 2-chamber view toward the midesophageal bicaval view. In addition, a 2.0 × 1.5 cm mass continuous with the aortic root abscess was noted, protruding into the RVOT adjacent to the pulmonic valve (Fig. 1) (Video clip 2, see Supplemental Digital Content 2, <http://links.lww.com/AA/A39>. Modified midesophageal aortic valve long-axis view demonstrating both left [LVOT] and right ventricular outflow tracts [RVOT]. The membranous portion of the interventricular septum [MIVS] is involved in the aortic root abscess with continuum of the inflammatory process into the RVOT [arrows]. Of note, the abscess is adjacent to the ventricular side of the pulmonic valve without invading the valve itself.). Using color flow and spectral Doppler in the upper esophageal aortic arch short-axis view, RVOT obstruction was not present and pulmonic valve function appeared normal (Fig. 2). No evidence of fistula formation or extension of the abscess to the mitral-aortic intervalvular fibrosa was noted on either 2-dimensional or color flow imaging. Biventricular function appeared normal.

Surgical repair included aortic root replacement with a 24-mm homograft aortic valve, a modified Cabrol procedure extending the left main coronary artery with a saphenous vein graft, RVOT debridement, and patch closure of a pulmonary artery ulceration not visualized on TEE. Because of the extensive surgical repair with prolonged extracorporeal circulation, intraaortic balloon counterpulsation was required for separation from cardiopulmonary bypass. After a complicated postoperative course, the patient died on the fifth postoperative day from multisystem organ failure.

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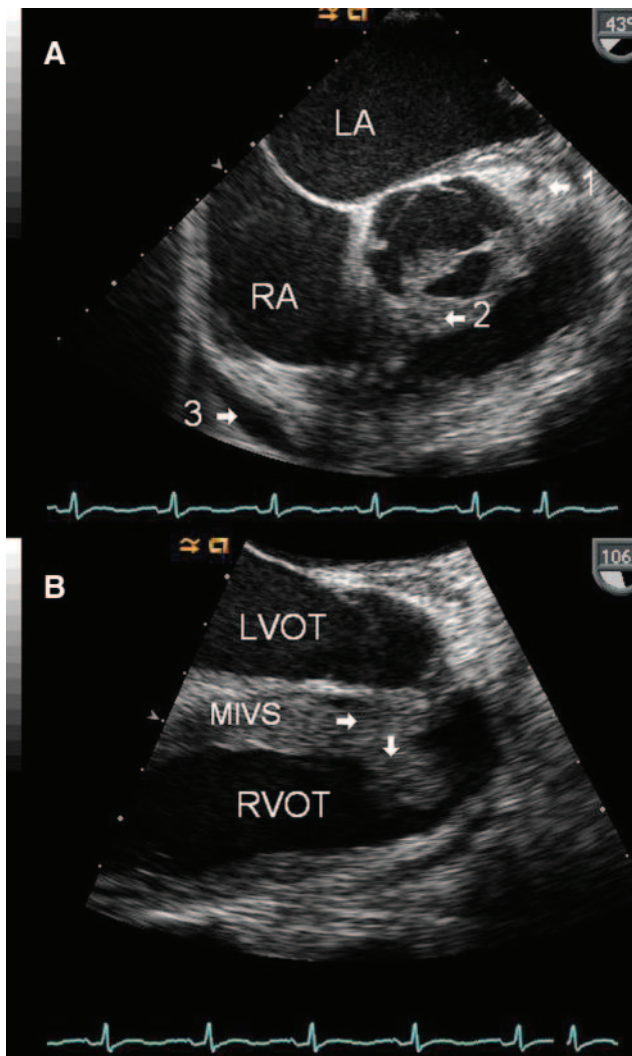


Figure 1. Panel A, Midesophageal aortic valve short-axis view: aortic root abscess is shown with thickening and increased echolucency of both areas of left (arrow 1) and right (arrow 2) proximal coronary arteries. Both bases of the right and left coronary leaflets are thickened; thickening of the free edge of the right coronary cusp with attached strands is noted. A small pericardial effusion is also present (arrow 3). Panel B, Modified midesophageal aortic valve long-axis view demonstrating both left (LVOT) and right ventricular outflow tracts (RVOT). The membranous portion of the interventricular septum (MIVS) is involved in the aortic root abscess with continuum of the inflammatory process into the RVOT (arrows). Of note, the abscess is adjacent to the ventricular side of the pulmonic valve without invading the valve itself.

DISCUSSION

Native aortic valve endocarditis presents with vegetations, usually involving the ventricular side of 1 or several aortic valve leaflets. Disease progression leads to development of aortic root abscess and periannular abscess extension into adjacent intracardiac structures in up to 9.8% of cases.¹ TEE is preferred over transthoracic echocardiogram for diagnosis because of increased sensitivity for detecting leaflet vegetations and perforations, as well as superior precision for defining perivalvular extension in the presence of a

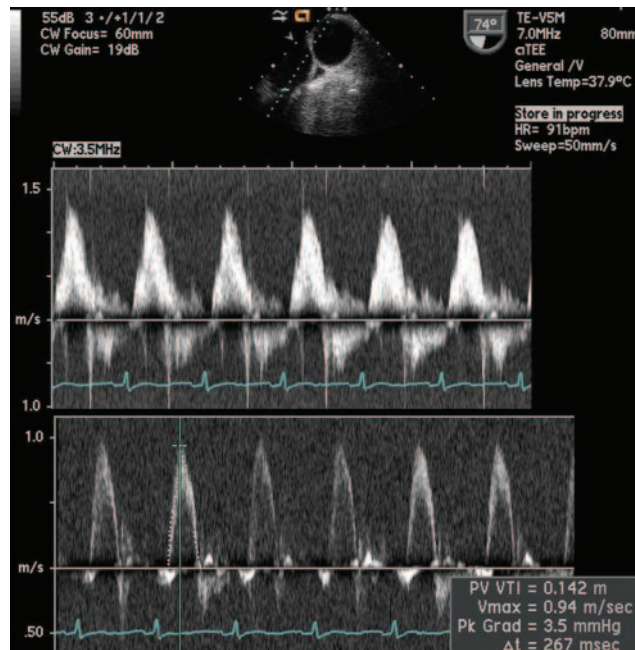


Figure 2. Upper esophageal aortic arch short-axis: both continuous wave Doppler (CWD) and pulsed wave Doppler (PWD) through the pulmonic valve demonstrated normal blood velocities, supporting normal valve function and absence of right ventricular tract obstruction. This view was chosen for optimal alignment of the ultrasound beam vector with blood flow. Of note, the mildly higher flow velocities of the CWD are explained by the smaller diameter of the pulmonary artery. The diastolic flow noted on the CWD (but not on the PWD) depicts tangential velocities sensed in the aortic arch.

myocardial abscess.² If aortic root abscess is suspected, midesophageal, aortic valve short- and long-axis imaging planes are recommended for complete evaluation, although stepwise angulation of the multiplane transducer may be necessary to detect fistula tracts.

Echocardiographic features of an aortic root abscess include abnormal thickening of the aortic annulus with echo-dense texture. Periannular abscess extension can occur in any direction with potential involvement of any cardiac chamber.³ If abscess extension in the right ventricle is noted, the RVOT should be investigated for signs of fixed or dynamic obstruction to blood flow.⁴ RVOT obliteration (using 2-dimensional and M-mode ultrasound) and flow aliasing in the RVOT (using color Doppler) are important qualitative echocardiographic findings consistent with RVOT obstruction. When present, further quantification by spectral Doppler examinations should be considered. The gradient can be determined using a pulmonary artery catheter to measure the systolic pulmonary artery pressure. From a midesophageal right ventricular inflow-outflow window, the peak systolic right ventricular pressure is estimated by investigation of the tricuspid regurgitant jet peak velocity, using the modified Bernoulli equation, and adding an estimate of the central venous pressure.

When present, RVOT obstruction is defined as significant when the peak right ventricular to pulmonary artery pressure gradient exceeds 25 mm Hg.⁴ Alternatively, a modified transgastric right ventricular inflow view may be used. Hereby, the TEE probe is first advanced to transgastric depth, anteflexing with 100°–120° angulation to display the transgastric inflow view. The multiplane angle is reduced stepwise until the RVOT develops, usually at 20°–40°. Using this view, the Doppler ultrasound vector can be sufficiently aligned to the direction of blood flow and reliable blood velocities and pressure gradients obtained.⁵ If the presumed obstruction is in close proximity to the pulmonic valve, as in this case, the upper esophageal aortic arch short-axis view usually provides an excellent imaging plane for investigation of blood flow. This view is developed starting from the upper esophageal long-axis view at 0°. The multiplane angle is rotated forward to 90° to display a cross-section of the aortic arch with a long section of the pulmonic valve and pulmonary artery (Fig. 2).

In this case, TEE confirmed that abscess propagation was directed anteriorly with involvement of the orifices of the right and left main coronary arteries, as well as invasion of the RVOT adjacent to the pulmonic valve. Surprisingly, the abscess did not extend into the mitral-aortic intervalvular fibrosa, an area demonstrated to be particularly susceptible to infectious

spread given the relative avascularity of this region.⁶ TEE imaging using multiple views and ancillary measurements (color flow and spectral Doppler) may provide important clinical information in the intraoperative management of severe endocarditis in general, and particularly with involvement of the aortic root.

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Clinician's Key Teaching Points

By Drs. Roman Sniecinski, Kent H. Rehfeldt, and Nikolaos J. Skubas:

- The spectrum of pathology associated with aortic valve endocarditis includes vegetations, leaflet perforations, and abscesses, which often extend to adjacent intracardiac structures. A unique feature of this case was extension of an aortic periannular abscess to the right ventricular outflow tract.
- Transesophageal echocardiogram examination is more sensitive than transthoracic echocardiography for detection of a thickened aortic annulus and pathologic, fluid-filled cavities and fistulous tracts; structures adjacent to the aortic annulus should be examined in the midesophageal short-axis and long-axis aortic valve views with stepwise angulation of the transducer.
- A periaortic valve abscess extending anteriorly can rarely cause obstruction of the right ventricular outflow tract. This can be evaluated using the midesophageal inflow and outflow view, the modified deep transgastric left ventricular view at 20°–40°, or the upper esophageal aortic arch short-axis views.

Color and spectral Doppler imaging across the right ventricular outflow tract should be performed; a peak systolic pressure gradient >25 mm Hg (using the simplified Bernoulli equation: $\Delta P = 4\text{velocity}^2$) is consistent with functional or anatomic right ventricular outflow obstruction.

Positive Intravascular Test Dose Criteria in Children During Total Intravenous Anesthesia with Propofol and Remifentanyl Are Different than During Inhaled Anesthesia

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BACKGROUND: The use of local anesthetic test doses is standard practice when performing regional anesthesia. When an intravascular test dose is administered during inhaled anesthesia, the heart rate does not increase in about 25% of children; altered T-wave amplitude is a better indicator. No studies have examined the criteria for a positive result during total IV anesthesia (TIVA) in children.

METHODS: We studied the effect of a simulated positive test dose on heart rate, arterial blood pressure, and T-wave amplitude in 17 ASA physical status I or II children receiving TIVA with propofol and remifentanyl. Bupivacaine 0.25% 0.1 mL/kg with epinephrine 1:200,000 was injected IV, and vital signs and electrocardiogram were continuously monitored. Increases of heart rate and arterial blood pressure >10% and T-wave amplitude >25% of baseline were considered clinically significant changes.

RESULTS: All subjects had increased systolic and diastolic blood pressure ($30.3\% \pm 11.7\%$ and $49.3\% \pm 16.7\%$), which peaked within 120 s. Heart rate increases >10% of baseline occurred in 73% of subjects. T-wave amplitude increased in 33.3%, was unchanged in 25%, and decreased in 41.7% of subjects.

CONCLUSIONS: A positive test dose during TIVA is best detected by increased arterial blood pressure. Twenty-seven percent of intravascular injections were missed using heart rate criteria. T-wave amplitude is not a reliable indicator of intravascular injection during TIVA. This is in marked distinction to what is seen during inhaled anesthesia.

(Anesth Analg 2010;110:41-5)

For >20 yr, the use of test doses of local anesthetics has been a standard practice when performing regional anesthesia. The technique was first described

by Moore and Batra¹ in awake adults. They determined that an IV injection of local anesthetic containing 15 μg of epinephrine resulted in a predictable increase of heart rate (mean increase of 31 bpm) that occurred within 23 s of injection and lasted approximately 30 s. This simulated the inadvertent IV injection of an epidural test dose and suggested that such test doses could be used to detect intravascular misplacement of an epidural catheter. Despite the widespread acceptance of this technique, no studies of test doses in either pediatric patients or in patients under general anesthesia were performed until 1990, when Desparmet et al.² used the same methodology in children receiving halothane. They found that IV injection of a test dose did not produce an increase of heart rate in 27% of the subjects, clearly an unacceptably high false-negative rate.

Subsequent studies by other investigators have confirmed the findings of Desparmet et al. and have shown similar results when using other inhalation anesthetics.³⁻⁵ Careful observation of the ST segment of the electrocardiogram (ECG) has been shown to detect IV injection with a higher degree of reliability than either heart rate changes or arterial blood pressure changes in children under general inhaled anesthesia.^{6,7}

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DMP is the principal investigator and was involved in the design and conduct of the study, data collection and analysis, and manuscript preparation. JZ helped in the design of the study, data collection and analysis, and manuscript preparation. KL helped with the conduct of the study, data collection, and analysis. ZP participated in the data analysis for the study.

Preliminary data from this study were presented at the Annual Meeting of the American Society of Anesthesiologists, October 26, 2004, Las Vegas, NV.

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The use of total IV anesthesia (TIVA) in both adults and children has increased in recent years with the introduction of new short-acting IV drugs such as propofol and remifentanyl. Although a long- or intermediate-acting opioid or nonsteroidal drug can be administered at the end of the procedure for postoperative analgesia, regional blockade, administered while the child is anesthetized, is often used for postoperative analgesia in children and has numerous advantages, including fewer undesirable side effects and a long duration of action. There are no published data on the efficacy of test doses to detect inadvertent intravascular injection of local anesthetic during TIVA in children. We studied the effect of an intravascular injection of bupivacaine with epinephrine on heart rate, T-wave amplitude, and arterial blood pressure to determine the reliability and the best indicator of a positive test dose during TIVA. We used the same methodology used in the investigations described above to determine whether standard test doses are effective at detecting an intravascular injection of local anesthetic.

METHODS

After local IRB approval, 17 ASA physical status I or II children, aged 8 mo to 12 yr, were enrolled in the study. Informed consent was obtained from the children's parents, and assent was obtained from children older than 7 yr. All children were scheduled to undergo elective surgical procedures under general anesthesia and were deemed suitable for TIVA with propofol (Baxter, New Providence, NJ) and remifentanyl (Abbott Laboratories, Abbott Park, IL) by the attending anesthesiologist responsible for their clinical care. Exclusion criteria were factors that might increase the risk of toxicity for local anesthetics and included age <6 mo, a history of cardiac disease or dysrhythmias, or a history of seizures. A premedication of oral midazolam (Roxane Laboratories, Columbus, OH) 0.3 mg/kg was given at the discretion of the attending anesthesiologist. Anesthesia was induced by inhalation of sevoflurane (Abbott Laboratories) in 40% oxygen/60% N₂O or, in 1 subject in whom IV access was in place, with 3.5 mg/kg of propofol. As soon as consciousness was lost, an IV cannula was placed, the sevoflurane was discontinued, and TIVA with remifentanyl and propofol was begun. The fresh gas flow was increased to at least 10 L/min to speed the washout of sevoflurane. Ten milliliters per kilogram of lactated Ringer's solution was rapidly administered. No neuromuscular blocking drugs, atropine, or other drugs were given. An end-tidal CO₂ value in the normal range was achieved either with spontaneous ventilation or pressure-limited ventilation.

Remifentanyl, 100 μg/mL, was freshly mixed in propofol at a concentration of 20 μg of remifentanyl per milliliter (10 mg) of propofol. The infusion was begun at 100 μg · kg⁻¹ · min⁻¹ of propofol/0.2 μg · kg⁻¹ · min⁻¹

of remifentanyl and controlled with a Medfusion 2010 syringe pump (Medex, Dublin, OH). The infusion was run for 10 min before the initiation of the study to allow for adequate washout of the sevoflurane and for stabilization of the TIVA.

After at least 10 min, when the end-tidal concentration of sevoflurane reached 0%, control values of heart rate, arterial blood pressure, and ECG were obtained. A simulated positive test dose of 0.1 mL/kg (3 mL maximum) of 0.25% bupivacaine with epinephrine (AstraZeneca, Wilmington, DE), 1:200,000 (0.25 mg/kg of bupivacaine and 0.5 μg/kg of epinephrine), was administered through the IV line at time 0. ECG (lead II), heart rate, and pulse oximetry were continuously monitored and recorded. Arterial blood pressure was measured by automated oscillometric cuff every 60 s. ECG was recorded on either a paper strip chart recorder (Subjects 1–12) or using a computerized data acquisition system, which digitized the ECG signal directly to a hard drive (Datex-Ohmeda s/5 Data Collect, Helsinki, Finland). Data were collected until all values returned to baseline (<3 min in all subjects). No other medications were administered until after the end of the study, and no surgical stimulation occurred during the study period.

The criteria set for positive test dose detection were as follows:

- Heart rate: increase of >10% from baseline,
- T-wave amplitude: change of >25% from baseline,
- Arterial blood pressure: increase of systolic or diastolic blood pressure of >10% from baseline.

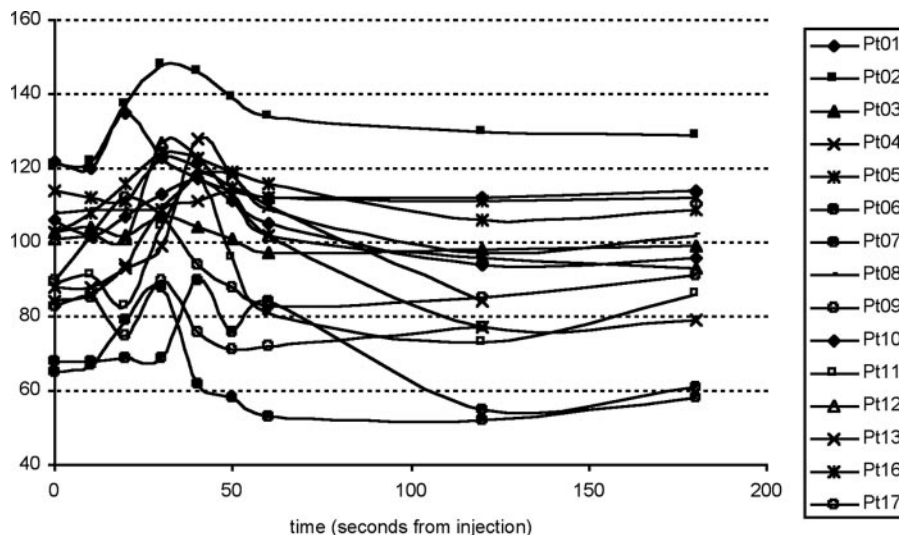
These values were chosen to reflect the smallest change that a clinician would be likely to easily detect by observation during clinical care and are consistent with criteria used in previous investigations of test doses during general anesthesia.

T-wave amplitude data were measured by hand from paper ECG strips or, when available digitally, using the measurement tools in the s/5 Data Collect program. The hand-measured data were measured in millimeters, and the digitally collected data in millivolts. The height of the T-wave was measured as the amount of deflection from the ST segment. The maximum change in T-wave amplitude (negative or positive) was measured after review of the entire strip chart or digital recording to identify the complex with the greatest change from the baseline value. T-wave change data are expressed in percent change from baseline.

Table 1. Demographic Data of Study Subjects

| Age | Sex | Weight |
|---|-------------------------|--|
| 5.02 ± 3.29 yr (range, 11 mo to 11 yr) | 73% Male, 23% female | 18.78 ± 8.49 kg (range, 10.6–41 kg) |

Figure 1. Heart rate response for each subject after IV injection of a test dose. All subjects had an increase in heart rate but 4 did not meet the 10% above baseline threshold set for a positive response.



Data were analyzed with SAS for Windows (SAS Institute, Cary, NC). Heart rate changes were evaluated with a signed rank test. A quadratic regression of the heart rate over the 60-s window after test dose injection was performed. Arterial blood pressure data were evaluated by a sensitivity analysis using a binomial proportion to determine confidence limits and by signed rank test. T-wave data were analyzed with 2-tailed *t*-tests, and upper and lower confidence intervals were determined.

RESULTS

Seventeen subjects were enrolled in the study (Table 1). Two subjects were eliminated from the analysis, one because of data recording malfunctions and the other because it was discovered after administration of the test dose that the left limb and arm ECG leads were inadvertently reversed. No adverse events occurred in any subject. Although the original intent was to enroll 60 subjects, a number based on power analysis of previous studies using this methodology, the IRB, at their annual review of the study, voiced concerns that the small transient arterial blood pressure increases placed our subjects at increased risk of adverse events. At this point, an interim analysis was performed, which showed that statistical significance had already been reached even with this small number of subjects, and enrollment in the study was concluded.

Heart Rate

Positive heart rate criteria (an increase of >10% from baseline) were met in only 73% of subjects, although an increase of some magnitude was seen in every subject (Fig. 1). Heart rate increased by a mean of 19.5% (95% confidence interval 14.5%–28.5%, $P < 0.0001$). In those whose heart rates increased >10%, that threshold was detected within 40 s of test dose injection (mean peak, 33 s) and returned to baseline by 60 s (Fig. 2).

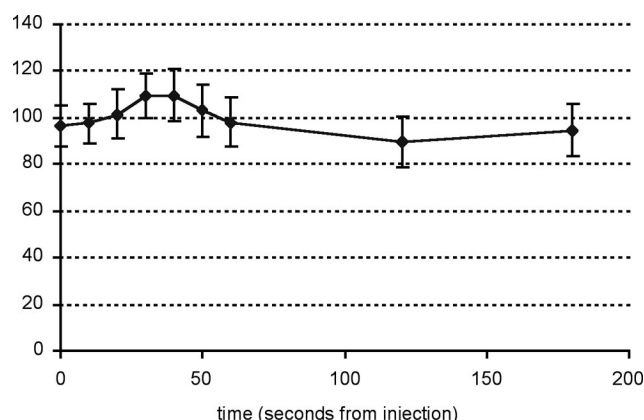


Figure 2. Mean heart rate after IV injection of a test dose (15 subjects). Error bars indicate ± 2 SEM.

T-Wave Amplitude

T-wave amplitude increased in 33.3%, was unchanged in 25%, and decreased in 41.7% of subjects ($P = 0.909$ by paired *t*-test) (Fig. 3).

Arterial Blood Pressure

Systolic blood pressure increased by a mean of 26% \pm 12.5% (95% confidence interval 19.5%–32.0%, $P < 0.0001$) and diastolic by 40.5% \pm 21.1% (95% confidence interval 29.8%–51.1%, $P < 0.0001$) of baseline values (Fig. 4). Diastolic blood pressure increased above the 10% threshold in all subjects studied, and systolic blood pressure did so in all but 1 subject, whose pressure increased by 9%. When heart rate did increase, it always preceded the increase in blood pressure; however, without continuous measurement of arterial blood pressure, we cannot determine this with surety. Increases in blood pressure always peaked within 120 s of test dose injection and returned to near baseline values within 180 s.

DISCUSSION

Previous reports of test doses administered during general inhaled anesthesia have noted that relying on

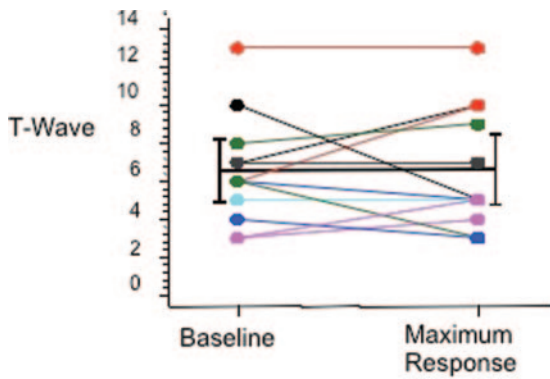


Figure 3. T-wave responses in individual subjects to IV injection of a test dose. The T-wave scale is in arbitrary units, and the pair of values for each subject denotes the maximum change of T-wave amplitude from baseline. The mean value is indicated by the dark line with the error bars (± 2 SEM).

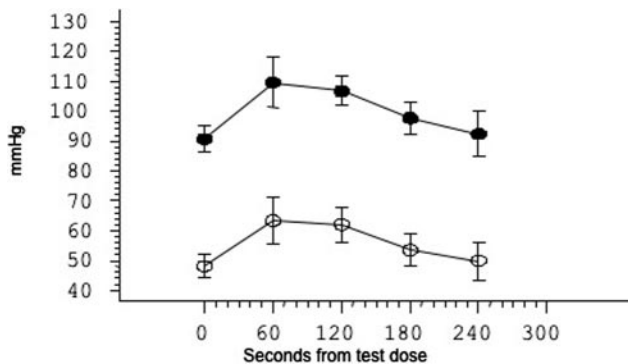


Figure 4. Mean systolic (closed circles) and diastolic (open circles) blood pressures after injection of a simulated intravascular test dose. Error bars indicate ± 2 SEM. The values at 60 and 120 s differ significantly from control at time 0 ($P < 0.0001$).

heart rate changes to detect intravascular injection carries a false-negative rate of approximately 25%. Our data obtained during TIVA with propofol and remifentanyl are similar. Changes in T-wave amplitude have been shown to be a reliable indicator during inhaled anesthesia, detecting 100% of IV injections during sevoflurane anesthesia and 90%–95% during halothane anesthesia.⁶ In our subjects, however, T-wave alterations were a completely unreliable and variable sign during TIVA. This also differs from an adult study during propofol and N₂O anesthesia, whereby subjects consistently had decreases in T-wave amplitude when a simulated positive test dose was administered.⁸

In our study, only arterial blood pressure was a reliable indicator of IV injection during propofol-remifentanyl TIVA in children. The diastolic blood pressure was a particularly sensitive indicator, increasing $>10\%$ in every subject. A $\geq 10\%$ increase over baseline systolic blood pressure was measured in 87% of our subjects, and all subjects evidenced a $>9\%$ increase. Oscillometric blood pressure measurements, which measure mean arterial blood pressure (the pressure at which oscillometric amplitude is greatest) and extrapolate the systolic and diastolic blood pressure using a computerized algorithm, may be inaccurate up to ± 5 mm Hg as

per the 1992 AAMI SP-10 standard but have been found to be closely correlated with both auscultated and intraarterial pressures under most circumstances.^{9,10} We obtained arterial blood pressure measurements at 1-min intervals and thereby may have missed the true peak pressure or overestimated the time to arterial blood pressure change that is seen after the injection of the test dose.

In our hospital and many other institutions, bupivacaine remains the most commonly used local anesthetic for regional blockade in children older than 6 mo of age. It is often our practice to use bupivacaine for the test dose, although lidocaine with epinephrine is also sometimes administered. We recommend some caution at extrapolating these results to a lidocaine and epinephrine test dose because these drugs might have different effects during TIVA, although the effects reported in studies with inhaled anesthesia are similar with both local anesthetics.

The reason for the inconsistent T-wave responses is not clear. Propofol has been shown to have no effect on atrioventricular node and sinoatrial nodal conduction in electrophysiologic studies in humans.¹¹ It has been demonstrated to decrease the dose of epinephrine required to induce dysrhythmias in dogs.¹² The effect of propofol on the Q-T interval and on the Q-T interval corrected for heart rate (Q-Tc) is controversial, although most investigators have found no change.^{13–15} It can increase the His-ventricular interval in the pig, but has no effect on repolarization.¹⁶ Remifentanyl increases vagal tone, resulting in bradycardia; we are not aware of any data regarding its effect on cardiac conduction.

Definitive conclusions from our data are limited by the small sample size because of the premature termination of enrollment. Nevertheless, statistical analysis showed that our results reached significance. Furthermore, the magnitude of changes measured, and, in the case of the T-wave data, the distribution of positive, negative, and no changes was easily detected clinically, suggesting that the results are applicable to the clinical setting. Although we did not enroll a control group or use a sham injection (e.g., administration of a saline bolus rather than a simulated test dose), the baseline period before any drug injection allowed each subject to serve as his or her own control. There was no stimulation or alteration in anesthetic depth during the baseline or study periods, thus no reason to suppose that physiologic changes measured were due to anything other than the administration of the simulated test dose. The previous studies using this methodology have all shown that false-positive findings do not occur under these conditions.

CONCLUSIONS

Our study found that, in marked distinction to what is seen during inhaled anesthesia, T-wave morphology is highly unreliable as an indicator of intravascular injection of bupivacaine with epinephrine

during TIVA with propofol and remifentanyl in children. Increases in arterial blood pressure, particularly diastolic blood pressure, seem to be the most reliable positive test dose criteria during TIVA under the conditions studied. Heart rate seems to have similar reliability during TIVA as during inhaled anesthesia and is inadequately sensitive to detect >75% of intravascular injections.

Despite the small sample size of this study, these data strongly suggest that the usual positive test dose criteria are inadequate to detect intravascular injection during TIVA and should not be relied upon. We recommend measuring arterial blood pressure at frequent intervals of no longer than 1 min after injection of the test dose and using the diastolic blood pressure as the most reliable criterion of an intravascular injection during TIVA. Although less potentially toxic levo-enantiomers of local anesthetics such as ropivacaine are becoming more frequently used, test dosing will continue to be necessary to detect intravascular misplacement of injection of even these safer drugs because they are not without risk of toxicity from intravascular injection.^{17,18} It is obvious that any test dose regimen is potentially fallible, and that our data are based on small numbers of subjects; therefore, incremental dosing is always advised. We look forward to further studies with larger numbers of subjects to corroborate our results.

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Monitored Anesthesia Care with Dexmedetomidine: A Prospective, Randomized, Double-Blind, Multicenter Trial

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BACKGROUND: Dexmedetomidine (DEX) is increasingly being used as a sedative for monitored anesthesia care (MAC) because of its analgesic properties, “cooperative sedation,” and lack of respiratory depression. In this randomized, multicenter, double-blind, Phase III Food and Drug Administration study, we evaluated the safety and efficacy of two doses of DEX for sedation of patients undergoing a broad range of surgical or diagnostic procedures requiring MAC.

METHODS: Three hundred twenty-six patients were randomized 2:2:1 to DEX 0.5 $\mu\text{g}/\text{kg}$, DEX 1 $\mu\text{g}/\text{kg}$, or saline placebo initial loading dose, followed by a maintenance infusion of 0.2–1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of DEX (or equivalent volume of saline) titrated to a targeted level of sedation (≤ 4 on the Observer’s Assessment of Alertness/Sedation Scale [OAA/S]). Study drug was started at least 15 min before placement of regional or local anesthetic block. Midazolam was given for OAA/S > 4 and fentanyl for pain. The primary end-point was the percentage of patients not requiring rescue midazolam.

RESULTS: Significantly fewer patients in the 0.5- and 1- $\mu\text{g}/\text{kg}$ DEX groups required supplemental midazolam compared with placebo (59.7% [80/134], 45.7% [59/129] vs 96.8% [61/63], respectively; $P < 0.001$) and at lower doses to achieve an OAA/S ≤ 4 before and during surgery compared with the saline group (1.4 and 0.9 mg vs 4.1 mg, respectively; $P < 0.001$, each group compared with placebo). Both DEX groups required significantly less fentanyl (84.8 and 83.6 μg vs 144.4 μg , respectively; $P < 0.001$, for both DEX groups versus placebo) for all surgical subtypes. Anesthesiologists indicated significantly increased ease of achieving and maintaining targeted sedation in both DEX groups compared with placebo with midazolam ($P < 0.001$). Patient satisfaction was significantly higher with DEX ($P \leq 0.009$, both groups versus placebo). Common adverse events with DEX were protocol-defined bradycardia and hypotension that were predominately mild to moderate in severity. The incidence of clinically significant respiratory depression (defined as a respiratory rate of < 8 or an oxygen saturation of $< 90\%$) was lower in DEX-treated patients ($P = 0.018$, for both groups versus placebo).

CONCLUSIONS: DEX is an effective baseline sedative for patients undergoing MAC for a broad range of surgical procedures providing better patient satisfaction, less opioid requirements, and less respiratory depression than placebo rescued with midazolam and fentanyl.

(Anesth Analg 2010;110:47–56)

The most commonly used medications for monitored anesthesia care (MAC) are midazolam, propofol, and fentanyl. Each of these drugs, however, causes respiratory depression.^{1,2} The most commonly reported adverse effects of midazolam are variability of patient

response and respiratory complications.² Combining midazolam with fentanyl or other opioids for MAC increases the risk for hypoxemia and apnea.¹ The addition of propofol may further exacerbate respiratory depression.³ A 2006 review of closed malpractice claims in the American Society of Anesthesiologists’ Closed Claim Database revealed oversedation leading to respiratory depression played a pivotal role in patient injuries during MAC.⁴ The adverse respiratory profile of benzodiazepines, propofol, and opioids, along with the stress response to surgery, create the need for a sedative drug

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that can be used safely during MAC in both healthy and high-risk patients, with limited adverse effects.

Dexmedetomidine (Precedex[®], Hospira, Lake Forest, IL) is a centrally acting α -2 receptor agonist that can be titrated to the desired level of sedation without significant respiratory depression.⁵⁻⁷ Dexmedetomidine has an analgesic-sparing effect, significantly reducing opioid requirements both during and after surgery.^{3,8-12} In addition, dexmedetomidine has a sympatholytic effect that can attenuate the stress response to surgery, mitigating tachycardia and hypertension.^{8,11} Because of its analgesic properties, "cooperative sedation," and lack of respiratory depression, dexmedetomidine is increasingly being used as a sedative for MAC.⁶ There have been several reports on the successful use of dexmedetomidine as the primary sedative drug for orthopedic, ophthalmic, dental, and plastic surgery, and for diagnostic procedures.¹¹⁻¹⁶

The safety and efficacy of dexmedetomidine in nonintubated patients undergoing MAC have not been rigorously evaluated in a large clinical study. We present the results of a prospective, multicenter trial that evaluated the safety and efficacy of dexmedetomidine as the primary sedative drug for nonintubated patients having MAC.

METHODS

This was a prospective, randomized, double-blind, placebo-controlled, Phase III study conducted at 26 investigational sites in the United States (ClinicalTrials.gov; NCT00398827). A placebo-controlled design was selected to comply with Food and Drug Administration requirements. The protocol was approved by the IRB of the study centers, and all patients provided written informed consent. Patients scheduled for elective surgeries and procedures performed in an operating room or procedure room and requiring MAC with an anesthesiologist in attendance were eligible for enrollment. Surgeries/procedures were expected to last at least 30 min and included orthopedic, ophthalmic, plastic, vascular stents, breast biopsies, hernias, arteriovenous fistulas, and excision of lesions. Eligible patients were ≥ 18 yr old, ASA physical status of I-IV, and required a local anesthetic block. Patients were excluded if they had received general anesthesia within 7 days before study entry, any experimental drug within 30 days before study drug administration, an α -2-agonist or antagonist within 14 days before the scheduled surgery/procedure, an IV opioid within 1 h, or an oral or IM opioid within 4 h of the start of study drug administration. Patients were also excluded if they required epidural or spinal anesthesia, or had any of the following: acute unstable angina, acute myocardial infarction documented by laboratory findings in the past 6 wk, heart rate (HR) < 50 bpm, systolic blood pressure (SBP) < 90 mm Hg, or third-degree heart block unless the patient had a pacemaker.

Patients were randomized in a 2:2:1 ratio to dexmedetomidine 0.5- $\mu\text{g}/\text{kg}$ load arm, 1- $\mu\text{g}/\text{kg}$ load arm, or saline placebo using a computer-generated randomization schedule. Two different loading groups were used for the main purpose of maintaining the blinding of the investigators with reference to the placebo group. The respective initial loading doses of 0.5 or 1.0 $\mu\text{g}/\text{kg}$ of dexmedetomidine or placebo were administered over 10 min followed by a maintenance infusion beginning at a rate of 0.6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Fifteen minutes after starting study drug, patients were assessed for level of sedation using the Observer's Assessment of Alertness/Sedation Scale (OAA/S)¹⁷ and any patient having a score > 4 received IV midazolam in 0.5 mg doses, repeated until OAA/S was ≤ 4 . After the initial loading dose, study drug was titrated from 0.2 to 1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of dexmedetomidine or saline equivalent volume to maintain score ≤ 4 . All subjects received a local anesthetic block before surgery/procedure (at least 15 min after beginning the drug infusion and when an OAA/S score ≤ 4 was observed). If a patient was not adequately sedated through titration, rescue midazolam could be administered as single IV boluses of 0.5 mg, repeated as needed to achieve an OAA/S score ≤ 4 . IV fentanyl, 25 μg boluses and repeated as necessary, could be given if a patient expressed a pain score of ≥ 3 during study drug infusion and ≥ 4 in the postanesthesia care unit (PACU) on a scale of 0-10 (0 = no pain, 10 = worst pain), or the investigator determined the presence of pain when verbal communication was not possible. At any time, if clinically indicated, the patient could be converted to an alternative sedative or anesthetic therapy and the study drug discontinued. OAA/S scores and all standard vital signs were obtained every 5 min throughout the study drug infusion and before the administration of any rescue midazolam. Study drug was discontinued when the patient left the operating room. Subjects remained in the PACU for a minimum of 1 h after discontinuation of study drug. Vital signs were recorded every 5 min for the first 15 min, then every 15 min for the next 45 min. The OAA/S and pain scores were assessed every 15 min while the patient was in the PACU.

Immediately after transfer to the PACU, the anesthesiologist rated the ease of maintenance of intraoperative sedation, respiratory stability, hemodynamic stability, and patient cooperation using visual analog scale scores. The patient's level of anxiety experienced before, during, and after the study drug infusion was assessed using the Anxiety Assessment Scale; scores range from 0 (no anxiety) to 10 (extreme anxiety). Patients were discharged when the Aldrete Score¹⁸ was ≥ 9 . Twenty-four hours after discontinuation of study drug, patients were visited or contacted by telephone to assess satisfaction with their anesthetic using the Iowa Satisfaction with Anesthesia Scale.¹⁹ The schematic of the overall study design is provided in Figure 1.

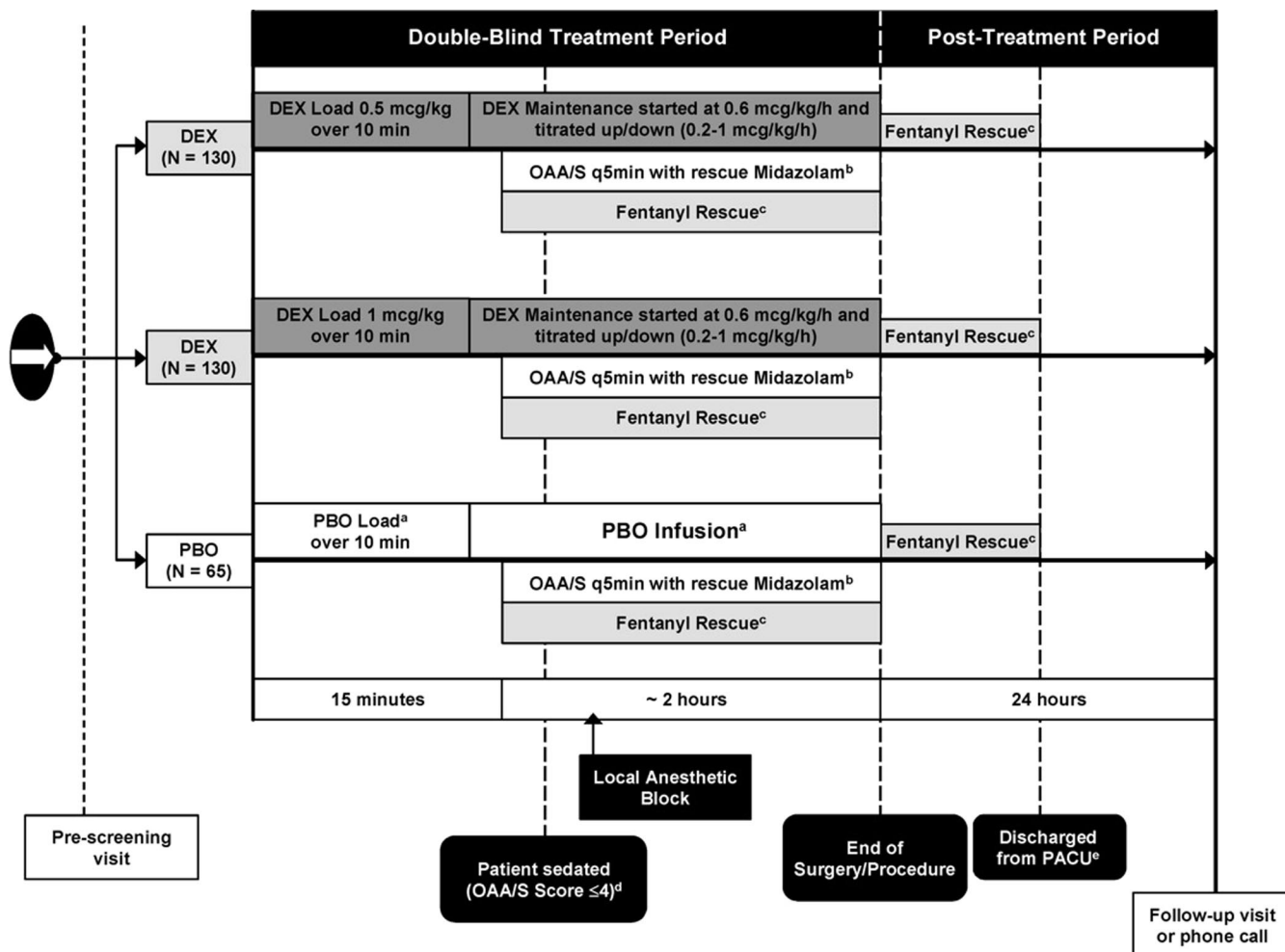


Figure 1. Study schema. ^aPlacebo group received sodium chloride at an infusion rate equivalent to the DEX groups. ^bBeginning 15 min after the start of study drug infusion and continuing throughout the surgery/procedure, rescue boluses of midazolam 0.5 mg were given for OAA/S >4 after titration of study drug. ^cBeginning 15 min after study drug infusion until the patient was discharged from the PACU, rescue boluses of fentanyl 25 μ g IV were given as needed for pain based on protocol-specified pain assessments. ^dThe patient was sedated (OAA/S \leq 4) before entry into the operating room, procedure room, or block room and before administration of local anesthetic block. ^eAt least 1 h after study drug had been discontinued. DEX = dexmedetomidine; PBO = placebo; OAA/S = Observer's Assessment of Alertness/Sedation Scale; PACU = postanesthesia care unit.

The primary efficacy end-point was the percentage of patients not requiring midazolam for rescue sedation based on achieving and/or maintaining an OAA/S score \leq 4. Secondary end-points included total amount of rescue midazolam, time from onset of study drug infusion to first dose of rescue midazolam, percentage of patients who converted to alternative sedative and/or anesthetic therapy because of treatment and rescue failure, time to recovery and readiness for discharge from the PACU, total amount of fentanyl required for pain control, incidence of postoperative nausea and vomiting in the PACU, protocol-defined hemodynamic stability (SBP time outside range + HR time outside range/study drug infusion period), and overall patient and anesthesiologist satisfaction. Safety was evaluated by monitoring adverse events, cardiac hemodynamic variables, laboratory tests, vital signs, and concomitant medications. Protocol-defined relative changes in arterial blood pressure (30% or more change from baseline, which was

determined as the average of three measurements 3 min apart), HR (30% or more change from baseline determined as for arterial blood pressure), and absolute respiratory depression (defined as respiratory rate of <8 or an oxygen saturation of <90%) were also assessed.

Statistical Analysis

All patients who received randomized study drug and had at least one postbaseline efficacy measurement were included in the intent-to-treat population. Safety analyses were performed on all patients who were randomized and received any study drug. For the primary efficacy end-point, statistical assessments comparing dexmedetomidine, 1- μ g/kg load arm versus placebo (primary analysis), and dexmedetomidine, 0.5- μ g/kg load arm versus placebo, were performed separately using the Cochran-Mantel-Haenszel test adjusting for surgery/procedure type. Statistical assessments comparing each dexmedetomidine group versus placebo for

total amount of rescue midazolam were performed separately using an analysis of variance model adjusted for surgical type. Subgroup analyses were performed according to surgical procedure. χ^2 tests were used to compare treatment differences in the percentage of patients reporting any treatment-emergent adverse event and for each system organ class for each dexmedetomidine arm versus placebo. Vital signs were assessed using a two-sample *t*-test for each dexmedetomidine arm versus placebo. A sample size of 250 patients was required to provide >99% power, assuming >70% of patients in the dexmedetomidine 1- μ g/kg group and <10% in the placebo group did not require rescue midazolam for proper sedation during study drug infusion to detect a difference among treatment groups. All statistical tests were two-sided and a *P* value ≤ 0.05 was considered statistically significant.

RESULTS

Three hundred seventy-one eligible patients were randomized. Of these, 326 patients were included in the intent-to-treat and safety analyses, with 134 in the dexmedetomidine 0.5- μ g/kg arm, 129 in the dexmedetomidine 1- μ g/kg arm, and 63 in the placebo arm (Fig. 2). Baseline characteristics were similar among treatment groups (Table 1). Mean (\pm SD) duration of study drug infusion was 97.0 \pm 52.5, 102.3 \pm 59.7, and 105.6 \pm 47.4 min for the 0.5- μ g/kg, 1- μ g/kg, and placebo arm, respectively.

Efficacy

Significantly more patients in the dexmedetomidine 1- μ g/kg group did not require rescue midazolam to achieve an OAA/S score ≤ 4 compared with the placebo group (54.3% [70/129] vs 3.2% [2/63]; *P* < 0.001; Fig. 3). The number of patients in the dexmedetomidine 0.5- μ g/kg group requiring supplemental midazolam (40.3% [54/134] vs 3.2% [2/63]; *P* < 0.001; Fig. 3) was also significantly higher than for the placebo group (*P* < 0.001). The percentage of patients not requiring rescue midazolam was significantly higher in both dexmedetomidine groups versus placebo according to all surgical subtypes, with the exception of the dexmedetomidine 0.5- μ g/kg pooled Subgroup 3 (breast biopsies, excision of lesions, and plastic surgical procedures). All but two patients in the placebo group received rescue midazolam and both underwent cataract surgery.

The mean total dose of rescue midazolam was significantly lower for the dexmedetomidine 0.5- and 1- μ g/kg groups than for the placebo group (1.4 and 0.9 mg vs 4.1 mg, respectively; *P* < 0.001 for each comparison; Fig. 3). Results for the pooled surgery subtypes also significantly favored both dexmedetomidine groups over placebo. The median length of time from the start of study drug until a rescue dose of midazolam was administered was significantly longer for both the 0.5- and 1- μ g/kg groups than for the

placebo group (40.0 and 114.0 min vs 20.0 min, respectively; *P* < 0.001 for each comparison). Significantly fewer patients in both dexmedetomidine groups required additional drugs besides midazolam for sedation than the placebo group. Two patients (1.6%) in the 1- μ g/kg group, four (3.0%) in the 0.5- μ g/kg group, and seven (11.1%) in the placebo group could not be sedated with protocol-specified amounts of study drug or rescue midazolam (0.2 mg/kg) and required additional sedation with propofol or general anesthesia to complete their surgical procedure (*P* < 0.02 for each comparison).

Significantly fewer patients required rescue fentanyl for pain during the infusion period for all surgeries in both the 0.5- and 1- μ g/kg groups compared with the placebo group (59.0% [79/134] and 42.6% [55/129] vs 88.9% [56/63], respectively; *P* < 0.001 for both comparisons; Table 2). Additionally, significantly higher doses of fentanyl were required for the placebo group during the infusion period compared with both dexmedetomidine 0.5- and 1- μ g/kg treatment groups (144.4 μ g vs 84.8 and 83.6 μ g, respectively; *P* < 0.001 for both comparisons; Table 2). More fentanyl was required in all surgical subgroups, except ophthalmic surgery, in the placebo arm than both dexmedetomidine treatment groups.

Median time to recovery and readiness for discharge from the PACU was 29.0 min for patients in the dexmedetomidine 0.5- μ g/kg group, 25.0 min for patients in the dexmedetomidine 1- μ g/kg group, and 14.0 min in the placebo group (*P* = 0.068). Significantly more patients in the placebo group required additional pain medication in the PACU than the dexmedetomidine 1- μ g/kg group (*P* \leq 0.048). The incidence of postoperative nausea and vomiting was not significantly different among treatment groups.

Results from the anesthesiologists' assessment showed significant differences favoring both dexmedetomidine groups compared with the placebo group for ease of maintenance of sedation (visual analog scale 2.8 and 2.2 cm vs 4.4 cm, respectively; *P* < 0.001 for each comparison). There were no significant differences in anesthesiologists' assessment of hemodynamic stability, respiratory stability, or patient cooperation. After surgery in the PACU, patients' mean anxiety scores were significantly lower in the 1- μ g/kg group than in the placebo group (1.0 vs 1.9; *P* = 0.007). The Iowa Satisfaction with Anesthesia Scale results showed that patients were significantly more satisfied in both dexmedetomidine groups versus placebo (*P* \leq 0.001; Table 3).

Safety

The most common adverse events during the infusion period were protocol-defined changes in arterial blood pressure, HR, and respiratory rate. The majority of adverse events were mild or moderate in severity. A small group of patients received drug interventions for changes in HR and/or arterial blood pressure (Table 4). There was no difference in the incidence of

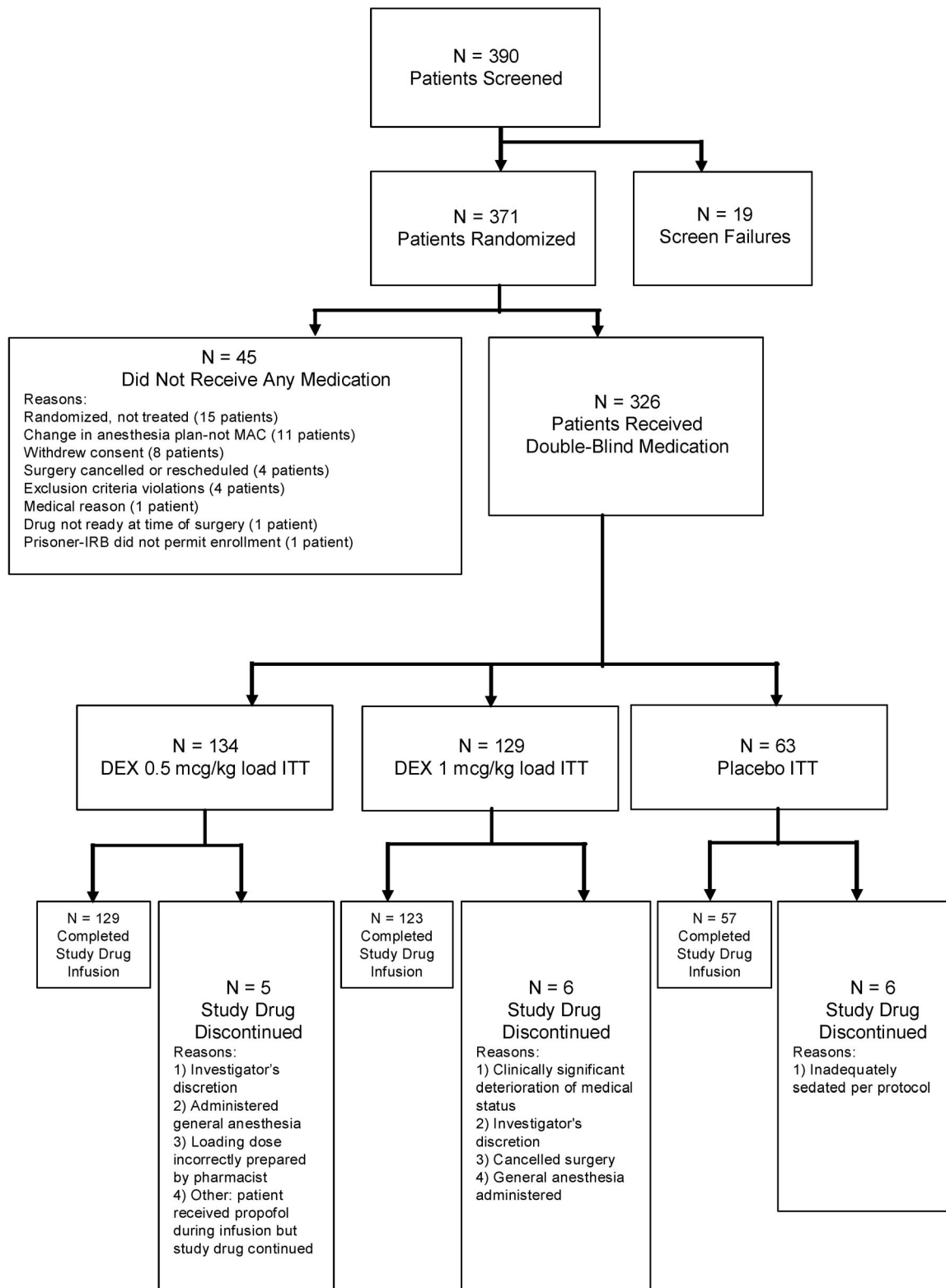


Figure 2. Patient disposition. ITT = intent-to-treat.

adverse events among treatment groups either intraoperatively or in the PACU. Three patients reported serious adverse events during the follow-up period and all were determined by the investigator to be unrelated to study drug. One placebo patient who was converted to general anesthesia experienced laryngospasm and pulmonary edema with placement of a

laryngeal mask airway. Seventeen patients (five patients in the 0.5- $\mu\text{g}/\text{kg}$ group, six in the 1- $\mu\text{g}/\text{kg}$ group, and six in the placebo group) prematurely discontinued study drug infusion (Fig. 2). There were no deaths during the study or follow-up period.

The mean decrease in SBP ($P \leq 0.043$) and diastolic blood pressure ($P < 0.001$) from baseline in both

Table 1. Baseline Characteristics by Treatment Group

| Variable | DEX 0.5 $\mu\text{g}/\text{kg}$ ($n = 134$) | DEX 1 $\mu\text{g}/\text{kg}$ ($n = 129$) | Placebo ($n = 63$) | <i>P</i> |
|---|---|---|----------------------|--------------|
| Age, yr | | | | ≥ 0.541 |
| Mean (SD) | 56.8 (16.51) | 53.8 (16.47) | 55.3 (16.69) | |
| Range | 18–93 | 19–88 | 20–80 | |
| Gender, <i>n</i> (%) | | | | ≥ 0.379 |
| Male | 68 (50.7) | 65 (50.4) | 36 (57.1) | |
| Female | 66 (49.3) | 64 (49.6) | 27 (42.9) | |
| Ethnic origin, <i>n</i> (%) | | | | ≥ 0.807 |
| Caucasian | 91 (67.9) | 74 (57.4) | 39 (61.9) | |
| African American | 23 (17.2) | 30 (23.3) | 14 (22.2) | |
| Asian | 1 (0.7) | 3 (2.3) | 1 (1.6) | |
| Hispanic | 18 (13.4) | 22 (17.1) | 9 (14.3) | |
| Other | 1 (0.7) | 0 | 0 | |
| ASA classification, <i>n</i> (%) | | | | ≥ 0.492 |
| I | 13 (9.7) | 22 (17.1) | 6 (9.5) | |
| II | 63 (47.0) | 57 (44.2) | 32 (50.8) | |
| III | 51 (38.1) | 40 (31.0) | 20 (31.7) | |
| IV | 7 (5.2) | 10 (7.8) | 5 (7.9) | |
| Baseline OAA/S scores ^a , <i>n</i> (%) | | | | ≥ 0.331 |
| 5 | 132 (98.5) | 129 (100.0) | 63 (100.0) | |
| 4 | 2 (1.5) | 0 | 0 | |
| 3 | 0 | 0 | 0 | |
| 2 | 0 | 0 | 0 | |
| 1 | 0 | 0 | 0 | |

DEX = dexmedetomidine; ASA = American Society of Anesthesiologists; OAA/S = Observer's Assessment of Alertness/Sedation Scale.

^a Baseline OAA/S scores: 5 = responds readily to name spoken in normal tone; 4 = responds only after mild prodding or shaking; 3 = responds only after name is called loudly and/or repeatedly; 2 = lethargic response to name spoken in normal tone; 1 = does not respond to mild prodding or shaking.

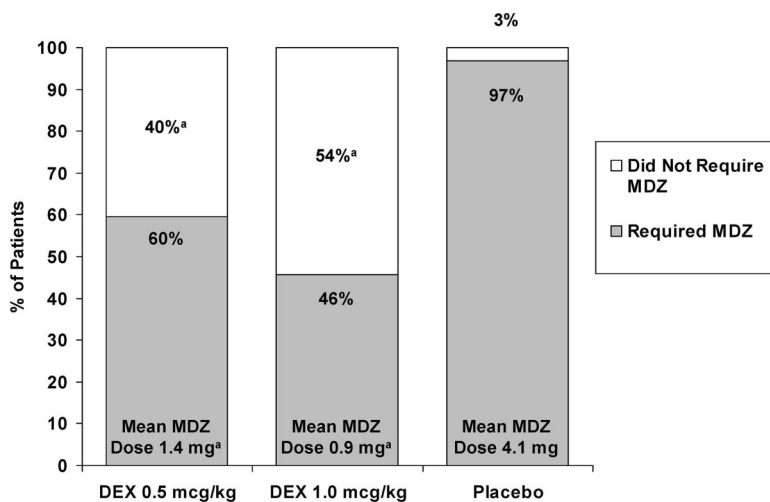


Figure 3. Percentage of patients who did not require rescue midazolam and mean midazolam dosage used in patients requiring rescue midazolam. ^a $P < 0.001$ versus placebo. *P* values for percentage of patients not requiring rescue MDZ based on Cochran-Mantel-Haenszel test, adjusting for surgery/procedure type; *P* values for mean dose of rescue midazolam based on one-way analysis of variance, adjusting for surgery/procedure type. DEX = dexmedetomidine; MDZ = midazolam.

dexmedetomidine groups was greater than the placebo group during the infusion and PACU periods, except for the difference between the 1- $\mu\text{g}/\text{kg}$ group and placebo group during the infusion period. The mean HR in both dexmedetomidine groups decreased significantly from baseline versus placebo during the infusion and PACU periods ($P < 0.001$). During study drug infusion, there was no difference in protocol-defined hemodynamic stability among the treatment groups. Fourteen patients (10.9%) in the 1- $\mu\text{g}/\text{kg}$ group and 16 patients (11.9%) in the 0.5- $\mu\text{g}/\text{kg}$ group received an intervention (titration of study drug, IV fluid bolus, or pharmacologic treatment) for treatment-related arterial blood pressure or HR adverse events during the infusion period, compared with two patients (3.2%) in the placebo group. The

coadministration of midazolam or fentanyl with dexmedetomidine was not associated with an increase in hypotension or bradycardia. There was no significant increase in the incidence of hypotension or bradycardia when dexmedetomidine was administered to patients taking chronic antihypertensive therapy, including β -blockers. Differences between the dexmedetomidine groups and the placebo group in cardiac monitoring, 12-lead electrocardiogram results, and laboratory profiles were unremarkable.

The incidence of absolute respiratory depression (defined as a respiratory rate of < 8 or an oxygen saturation of $< 90\%$) was significantly lower in both the 0.5- and 1- $\mu\text{g}/\text{kg}$ dexmedetomidine groups compared with placebo during the infusion period (3.7% and 2.3% vs 12.7%, respectively; $P = 0.018$). The

Table 2. Fentanyl Requirements During Surgery According to the Surgical Subgroups

| Total dose of fentanyl (μg) | DEX 0.5 $\mu\text{g}/\text{kg}$ load | <i>P</i> * | DEX 1 $\mu\text{g}/\text{kg}$ load | <i>P</i> * | Placebo |
|---|--------------------------------------|------------|------------------------------------|------------|---------|
| All surgeries | | | | | |
| <i>n</i> | 79 | | 55 | | 56 |
| Mean | 84.8 | <0.001 | 83.6 | <0.001 | 144.4 |
| SD | 52.9 | | 52.7 | | 100.1 |
| Pooled Type 1 (orthopedics) | | | | | |
| <i>n</i> | 38 | | 39 | | 20 |
| Mean | 50.1 | 0.0001 | 37.2 | <0.0001 | 128.8 |
| SD | 56.42 | | 49.29 | | 90.06 |
| Pooled Type 2 (ophthalmic) | | | | | |
| <i>n</i> | 34 | | 35 | | 18 |
| Mean | 19.1 | 0.0048 | 8.6 | 0.0002 | 57.6 |
| SD | 29.55 | | 25.68 | | 64.64 |
| Pooled Type 3 (breast biopsies, excision of lesions, and plastic surgical procedures) | | | | | |
| <i>n</i> | 38 | | 34 | | 15 |
| Mean | 67.8 | <.0001 | 56.6 | 0.0001 | 151.7 |
| SD | 55.11 | | 66.09 | | 85.81 |
| Pooled Type 4 (arteriovenous fistulas, vascular stents, and other) | | | | | |
| <i>n</i> | 24 | | 21 | | 10 |
| Mean | 65.5 | 0.0002 | 44.0 | <0.0001 | 220.0 |
| SD | 78.81 | | 59.11 | | 137.84 |

Fentanyl was administered for pain score >3 during study drug infusion. Significantly less fentanyl was administered in both dexmedetomidine groups.
DEX = dexmedetomidine.

* *P* value from analysis of variance model comparing each DEX arm versus the placebo arm.

Table 3. Overall Patient Assessment of Satisfaction

| Patient assessment ^a | DEX 0.5 $\mu\text{g}/\text{kg}$ mean (SD) (<i>n</i> = 134) | <i>P</i> * | DEX 1 $\mu\text{g}/\text{kg}$ mean (SD) (<i>n</i> = 129) | <i>P</i> * | Placebo mean (SD) (<i>n</i> = 63) |
|--|---|------------|---|------------|------------------------------------|
| 1—I threw up or felt like throwing up | 2.2 (1.67) | 0.959 | 2.2 (1.70) | 0.970 | 2.2 (1.74) |
| 2—I would have the same anesthetic again | 2.2 (1.32) | <0.001 | 1.8 (2.02) | 0.054 | 1.2 (2.35) |
| 3—I itched | 2.4 (1.26) | 0.064 | 2.4 (1.34) | 0.051 | 2.0 (1.76) |
| 4—I felt relaxed | 1.8 (1.71) | 0.009 | 1.9 (1.64) | 0.002 | 1.0 (2.44) |
| 5—I felt pain | 1.6 (1.98) | <0.001 | 1.3 (2.16) | 0.002 | 0.3 (2.28) |
| 6—I felt safe | 2.1 (1.40) | 0.409 | 2.3 (1.33) | 0.092 | 1.9 (1.68) |
| 7—I was too hot or cold | 1.9 (1.79) | 0.792 | 2.1 (1.69) | 0.264 | 1.8 (1.83) |
| 8—I was satisfied with the anesthesia care | 2.5 (1.06) | 0.007 | 2.6 (0.90) | <0.001 | 1.9 (1.82) |
| 9—I felt pain during surgery | 1.3 (2.11) | 0.159 | 1.8 (1.91) | 0.006 | 0.9 (2.33) |
| 10—I felt good | 1.7 (1.72) | 0.075 | 1.8 (1.66) | 0.019 | 1.2 (2.17) |
| 11—I hurt | 1.8 (1.89) | 0.002 | 1.9 (1.83) | <0.001 | 0.8 (2.36) |
| Overall ISAS score | 2.0 (0.97) | <0.001 | 2.0 (0.97) | <0.001 | 1.4 (1.39) |

DEX = dexmedetomidine; ISAS = Iowa Satisfaction with Anesthesia Scale.

^a For items 1, 3, 5, 7, 9, and 11, the scores are reassigned as follows: +3 = disagree very much; +2 = disagree moderately; +1 = disagree slightly; -1 = agree slightly; -2 = agree moderately; -3 = agree very much. For items 2, 4, 6, 8, and 10, the scores are reassigned as follows: -3 = disagree very much; -2 = disagree moderately; -1 = disagree slightly; +1 = agree slightly; +2 = agree moderately; +3 = agree very much. The Overall ISAS score is the mean of all reassigned item scores. The higher score indicates more favorable outcome.

* *P* values from analysis of variance model adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

Table 4. Patients with Cardiovascular Adverse Events Who Received Interventions During Study Drug Infusion

| Reason for intervention ^a | DEX 0.5 $\mu\text{g}/\text{kg}$ <i>n</i> (%) (<i>N</i> = 134) | <i>P</i> * | DEX 1 $\mu\text{g}/\text{kg}$ <i>n</i> (%) (<i>N</i> = 129) | <i>P</i> * | Placebo <i>n</i> (%) (<i>N</i> = 63) |
|--------------------------------------|--|------------|--|------------|---------------------------------------|
| Hypertension | | | | | |
| Infusion period | 3 (2.2) | 0.336 | 1 (0.8) | 0.069 | 3 (4.8) |
| Hypotension | | | | | |
| Infusion period | 16 (11.9) | 0.046 | 11 (8.5) | 0.166 | 2 (3.2) |
| Tachycardia | | | | | |
| Infusion period | 0 | 0.144 | 0 | 0.151 | 1 (1.6) |
| Bradycardia | | | | | |
| Infusion period | 1 (0.7) | 0.492 | 6 (4.7) | 0.082 | 0 |

DEX = dexmedetomidine.

^a Intervention for hypertension, hypotension, tachycardia, and bradycardia had occurred if these adverse events (or equivalent) were recorded, and the action taken was any value other than "None." Interventions were titration of study drug, IV fluid bolus, or pharmacologic.

* *P* values based on Pearson χ^2 test comparing each DEX arm versus the placebo arm.

coadministration of midazolam or fentanyl in both dexmedetomidine groups was not associated with increased absolute respiratory depression or a need for intervention for respiratory depression. No patient in any of the three groups received a reversal drug for the opioid or midazolam.

DISCUSSION

Dexmedetomidine was effective and well tolerated for sedation of patients requiring MAC. Efficacy results showed that significantly fewer patients in both the 0.5- and 1- $\mu\text{g}/\text{kg}$ dexmedetomidine groups required supplemental midazolam or fentanyl for sedation or analgesia. The mean total dose of rescue midazolam used to achieve and/or maintain the targeted sedation level was significantly lower in both dexmedetomidine groups: 0.9 mg for dexmedetomidine 1 $\mu\text{g}/\text{kg}$ and 1.4 mg for dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ compared with 4.1 mg for the placebo group. The percentage of subjects who required rescue fentanyl for analgesia during the infusion period was significantly lower for both dexmedetomidine groups (42.6% of 1 $\mu\text{g}/\text{kg}$ and 59.0% of 0.5 $\mu\text{g}/\text{kg}$ dexmedetomidine subjects) compared with 88.9% of placebo subjects ($P < 0.001$ for both comparisons); and the dose of fentanyl during study drug infusion was significantly lower in both dexmedetomidine groups, 83.6 and 84.8 μg of fentanyl for the dexmedetomidine 1 $\mu\text{g}/\text{kg}$ and 0.5 $\mu\text{g}/\text{kg}$, respectively, compared with 144.4 μg of fentanyl in the placebo group ($P < 0.001$ for each comparison). Significantly fewer subjects required postoperative analgesics in the dexmedetomidine 1- $\mu\text{g}/\text{kg}$ group than in the placebo group ($P = 0.025$). Patients in both dexmedetomidine groups expressed significantly greater satisfaction than the placebo group rescued with midazolam and fentanyl.

An important finding in this trial was the higher incidence of clinically significant respiratory depression in the placebo group as compared with both dexmedetomidine groups. Despite following a protocol with clearly defined variables for administering midazolam or fentanyl, 13.1% and 16.1% of patients in the placebo group who received midazolam with fentanyl, respectively, had an intervention for respiratory depression and 12.7% had a documented oxygen saturation $<90\%$ or respiratory rate <8 . This may be attributed to the significantly higher doses of midazolam and fentanyl that were required for sedation and analgesia in the placebo group versus the dexmedetomidine treatment groups. The doses of midazolam and fentanyl that were used may have been due to the study design although other trials have demonstrated similar findings or have shown no increase in respiratory complications between dexmedetomidine and midazolam with fentanyl.^{12,13} The analgesic-sparing effect of dexmedetomidine demonstrated herein and in other studies could potentially reduce the risk of developing respiratory depression and its related sequelae.^{5,8,12,20,21}

In a study by Alhashemi¹⁴ evaluating the use of dexmedetomidine for cataract surgery and by Zeyneloglu et al.²² in patients undergoing lithotripsy, the time for recovery and discharge from PACU was longer with dexmedetomidine. Although not statistically or clinically significant, the time for recovery and readiness for discharge from the PACU in our study was longer for both dexmedetomidine groups than the placebo group. Readiness for discharge may have been longer in the dexmedetomidine groups due to the fact that to maintain the blind in our study all groups had their infusions continued until the end of the surgery. It is expected that in standard practice an infusion such as dexmedetomidine would have been tapered before the end of surgery. In general, an infusion drug, such as dexmedetomidine, may be more difficult to use compared with bolus drugs in terms of when to stop the infusion, the time required to change dosage, and the need for an initial loading dose given over 10 min.

Both patient and anesthesiologist satisfaction and comfort were better with dexmedetomidine than placebo. Dexmedetomidine-treated patients were significantly more satisfied with their anesthetic than patients in the placebo group, and patients in the 1- $\mu\text{g}/\text{kg}$ group had significantly less postoperative anxiety after their MAC procedure. Higher satisfaction scores for dexmedetomidine compared with midazolam have been reported in other trials as well.^{14–16} In addition, anesthesiologists indicated that the ease of achieving and maintaining the targeted sedation level was significantly better in both dexmedetomidine groups compared with the placebo group using midazolam.

Dexmedetomidine was well tolerated in a variety of age groups and populations for a broad range of surgical and diagnostic procedures, and the incidence of treatment-emergent adverse events was similar among patients receiving dexmedetomidine or placebo. Overall, dexmedetomidine caused a predictable and manageable decrease in HR and arterial blood pressure. Protocol-defined hypotension was the most common adverse event in dexmedetomidine-treated patients during the infusion period; however, all cases were mild or moderate in severity and responded to intervention, when indicated. Additionally, no significant differences were noted for the rate of treatment of hypotension or bradycardia intraoperatively, however, interventions were increased in the PACU. McCutcheon et al.²⁰ found that dexmedetomidine, when compared with midazolam and fentanyl in carotid surgery patients, was associated with fewer interventions for hypertension and tachycardia. The effect of reducing HR and arterial blood pressure could be beneficial for patients at risk for cardiac morbidity because perioperative tachycardia and hypertension are associated with adverse cardiac outcomes in the postoperative period.^{23,24}

The surgical procedures that were studied in this trial were notably diverse, and it is possible that

dexmedetomidine may prove more suitable for some procedures than others. For example, a previous study of dexmedetomidine sedation during colonoscopy reported more adverse events in this population.²⁵ Although one study reported better patient cooperation during cataract surgery with dexmedetomidine than with midazolam, another reported more hypotension and delayed recovery room discharge.^{11,26} We believe that additional trials delineating the advantages and disadvantages of dexmedetomidine in specific procedures and populations are justified.

In conclusion, dexmedetomidine at the doses studied is a well tolerated, safe, and effective primary sedative alternative to traditional benzodiazepine/opioid combinations in patients undergoing MAC for a variety of surgical procedures. Using dexmedetomidine as the primary sedative permits significantly reduced requirements for both midazolam and fentanyl. Within the confines of the design of our study, dexmedetomidine-treated patients had a lower incidence of clinically relevant respiratory depression and significantly better patient satisfaction. Mean arterial blood pressure and HR were significantly lower in dexmedetomidine-treated patients compared with placebo patients receiving midazolam and fentanyl.

APPENDIX

The members of the MAC Study Group are as follows: Loma Linda University Medical Center, Loma Linda, CA: Martin W. Allard; New York University Medical Center, New York, NY: Alex Y. Bekker; The Ohio State University Medical Center, Columbus, OH: Sergio D. Bergese; University of Miami, Miami, FL: Keith A. Candiotti; Crossroads Research, Inc., Owings Mills, MD: Eric L. Diamond; University of Alabama at Birmingham, Birmingham, AL: Dennis D. Doblak; VA Medical Center, Milwaukee, WI: Thomas J. Ebert; Cleveland Clinic Foundation, Cleveland, OH: Marc Feldman; University of Missouri Health Care, Columbia, MO: Robert B. Fisher; Duke University Medical System, Durham, NC: Tong J. Gan; University of Miami, Miami, FL: Steven Gayer; Chesapeake Research Group, LLC, Pasadena, MD: Ira J. Gottlieb; William Beaumont Hospital, Royal Oak, MI: Craig T. Hartrick; Medical University of South Carolina, Charleston, SC: Gary R. Haynes; VA North Texas Health Care System, Dallas, TX: Fima Lenkovsky; VA Medical Center, Durham, NC: Terri Monk; University of Pittsburgh, Pittsburgh, PA: Paul A. Moore; University of Virginia, Charlottesville, VA: Thomas N. Pajewski; Brigham and Women's Hospital, Boston, MA: Beverly K. Philip; Baylor University Medical Center, Dallas, TX: Michael A.E. Ramsay; Miami Clinical Trials, South Miami, FL: Ruben Ricardo; The University of Texas M.D. Anderson Cancer Center, Houston, TX: Bernhard J.C.J. Riedel; Scott and White Memorial Hospital, Temple, TX: Charles R. Roberson; Beth Israel Deaconess Medical Center, Boston, MA: Fred E. Shapiro; The Mount Sinai School of Medicine, New York,

NY: Jeffrey H. Silverstein; The Johns Hopkins Hospital, Baltimore, MD: Tracey L. Stierer.

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ANNOUNCEMENT

Nominations Sought for Mentoring Excellence in Research Award

FAER is seeking nominations for the 2010 FAER Award for Mentoring Excellence in Research. This award was created to ensure that the value of outstanding mentors is recognized and to encourage, develop and retain these valuable individuals in our specialty.

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The deadline for nominations is March 31, 2010. Details on the nomination process and a nomination form are available at www.faer.org.

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Anesthetic Sensitivity of the *Gloeobacter violaceus* Proton-Gated Ion Channel

Yun Weng, PhD*

Liya Yang, PhD*

Pierre-Jean Corringer, PhD†

James M. Sonner, MD*

A prokaryotic member of the γ -aminobutyric acid type A receptor superfamily (GLIC) was recently cloned from the cyanobacterium *Gloeobacter violaceus*, its function characterized, and its 3-dimensional x-ray diffraction crystal structure determined. We report its modulation by 9 anesthetics using 2-electrode voltage clamping in *Xenopus laevis* oocytes. Desflurane, halothane, isoflurane, sevoflurane, and propofol inhibited currents through GLIC at and below concentrations used clinically. Hill numbers averaged 0.3, indicating negative cooperativity or multiple sites or mechanisms of action. A 2-site model fit the data for desflurane and halothane better than a 1-site model. Xenon and etomidate modulated GLIC at or above clinical concentrations, with no cooperativity. Ethanol and nitrous oxide did not modulate GLIC at surgical anesthetic concentrations. These investigations lay the groundwork for further structural and functional studies of anesthetic actions on GLIC.

(Anesth Analg 2010;110:59–63)

Clinical concentrations of anesthetics modulate the function of pentameric ligand-gated ion channels from the γ -aminobutyric acid type A (GABA_A) superfamily. We studied the modulation of a prokaryotic member of this superfamily, the proton-gated cation channel from the cyanobacterium *Gloeobacter violaceus* (GLIC)¹ by halothane, isoflurane, sevoflurane, desflurane, xenon, etomidate, propofol, ethanol, and nitrous oxide. We sought to identify anesthetics that modulate GLIC and that might therefore merit further investigation by structural methods. We found that, similar to GABA_A receptors, GLIC is modulated by a large number of anesthetics. Similar to neuronal nicotinic acetylcholine receptors, it is very potently modulated by some of these drugs.

METHODS

The Institutional Animal Care and Use Committee at the University of California, San Francisco, approved all studies on animals.

Materials

Isoflurane, sevoflurane, and desflurane were obtained from Baxter Healthcare Corporation (Deerfield, IL). Halothane was from Halocarbon (River Edge, NJ). Etomidate (>95%) was from ChemPacific (Baltimore, MD). Xenon was from SynQuest Laboratories (Alachua, FL). United States Pharmacopeia–grade nitrous oxide was from Airgas (San Francisco, CA). Propofol (97%) and other reagents were purchased from Sigma-Aldrich (St. Louis, MO).

Oocyte Expression and 2-Electrode Voltage Clamp Recording

GLIC was expressed in *Xenopus laevis* oocytes and studied by 2-electrode voltage clamping following methods described previously.^{1,2}

Oocytes were voltage clamped at -60 mV. Currents were elicited by application of frog Ringer's solution² at a pH that produced 20% of the maximal effect (EC₂₀; approximately pH 5.5). For each oocyte, stable inward currents were verified by application of protons until a plateau in current was achieved. Anesthetic was then applied to oocytes for 100 s, followed by coapplication of protons with anesthetic. Return to the baseline response to protons after washout of anesthetic was confirmed in all oocytes.

Data Analysis

Anesthetic effect was calculated as the percent change in current in oocytes clamped at -60 mV

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YW and LY helped to design the study, conducted the study, and reviewed the manuscript. PJC was involved in study design and manuscript preparation. JMS participated in study design, data analysis, and manuscript preparation.

Reprints will not be available from the author.

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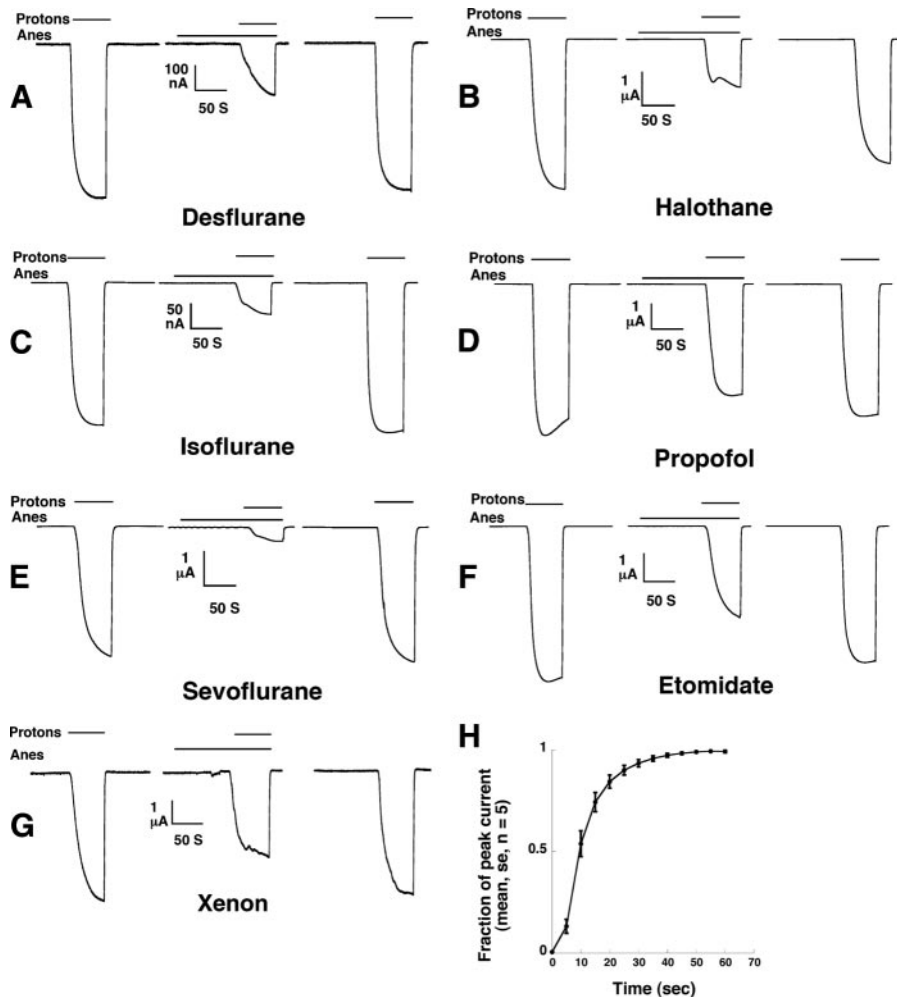


Figure 1. Current tracings are shown for 0.5 mM desflurane (A), 0.25 mM halothane (B), 0.3 mM isoflurane (C), 1 μ M propofol (D), 0.3 mM sevoflurane (E), 50 μ M etomidate (F), and 80% atm xenon (G), all of which inhibit currents through the *Gloeobacter violaceus* ion channel (GLIC). The first current tracing in each group shows the activation of the channel by protons at their EC_{20} . The second current tracing is obtained with a 100-s washin of anesthetic followed by co-application of anesthetic and protons. The final tracing shows currents activated by protons after washout of anesthetic. "Anes" denotes the time span during which anesthetic was applied. "Protons" denotes the time when superfusate at the proton EC_{20} was applied. The fraction of the plateau current achieved as a function of time (average of 5 oocytes) is shown in (H). Mean currents and standard errors are displayed in (H).

during anesthetic and proton coadministration versus currents when protons alone were applied. The change in channel currents upon application of anesthetic was fit to a Hill equation:

$$\text{Change in current (in \%)} = -100 / (1 + 10^{(\log IC_{50} - x)^n})$$

where x is the concentration of anesthetic, n is the Hill coefficient, and IC_{50} is the concentration of anesthetic that produces a 50% change in current, and to a 2-site model:

$$\text{Change in current} = A + (B - A) [I_1 / (1 + 10^{[x - \log IC_{50(1)]})} + I_2 / (1 + 10^{[x - \log IC_{50(2)]})}]$$

where $IC_{50(1)}$ and $IC_{50(2)}$ are the affinities of the anesthetics for the 2 sites, I_1 and I_2 are the percent inhibition attributable to each site, and B and A are the maximum and minimum asymptotes of the curve.

Data were analyzed using SPSS version 16.0 (Chicago, IL) and GraphPad Prism 5 (La Jolla, CA).

RESULTS

Current tracings are shown in Figure 1. GLIC was inhibited by the halogenated inhaled anesthetics and propofol. Figure 2 shows the concentration-response

curves. Hill numbers and IC_{50} s for modulation of GLIC, and anesthetic EC_{50} in animals, are shown in Table 1.³⁻⁸

Xenon 0.8 atm, which is slightly above the minimum alveolar concentration (MAC) of xenon in humans,³ inhibited currents. Etomidate was inhibitory at concentrations above those used to achieve anesthesia (Fig. 3 and Table 1).

Ethanol had no effect on GLIC at 200 mM (data not shown), which is the upper limit of anesthetizing concentrations in animals.⁴ Nitrous oxide 1 atm, which is approximately MAC in humans,⁵ had no effect compared with 1 atm nitrogen (data not shown).

The 2-site model fit the data better than the Hill equation for desflurane ($F_{3,35} = 3.379$, $P = 0.029$) and halothane ($F_{3,34} = 3.112$, $P = 0.039$).⁹ For desflurane, $IC_{50(1)} = 0.00001$ mM (95% confidence interval [CI]: 0.0000004–0.0002 mM), $IC_{50(2)} = 0.3$ mM (95% CI: 0.15–3.0 mM), $I_1 = 0.15$, and $I_2 = 0.85$. For halothane, $IC_{50(1)} = 0.0003$ mM (95% CI: 0.000002–0.06 mM), $IC_{50(2)} = 1.1$ mM (95% CI: 0.1–12 mM), $I_1 = 0.23$, and $I_2 = 0.77$.

DISCUSSION

Anesthetics were clustered into 3 groups based on their modulation of GLIC. One group consisted of

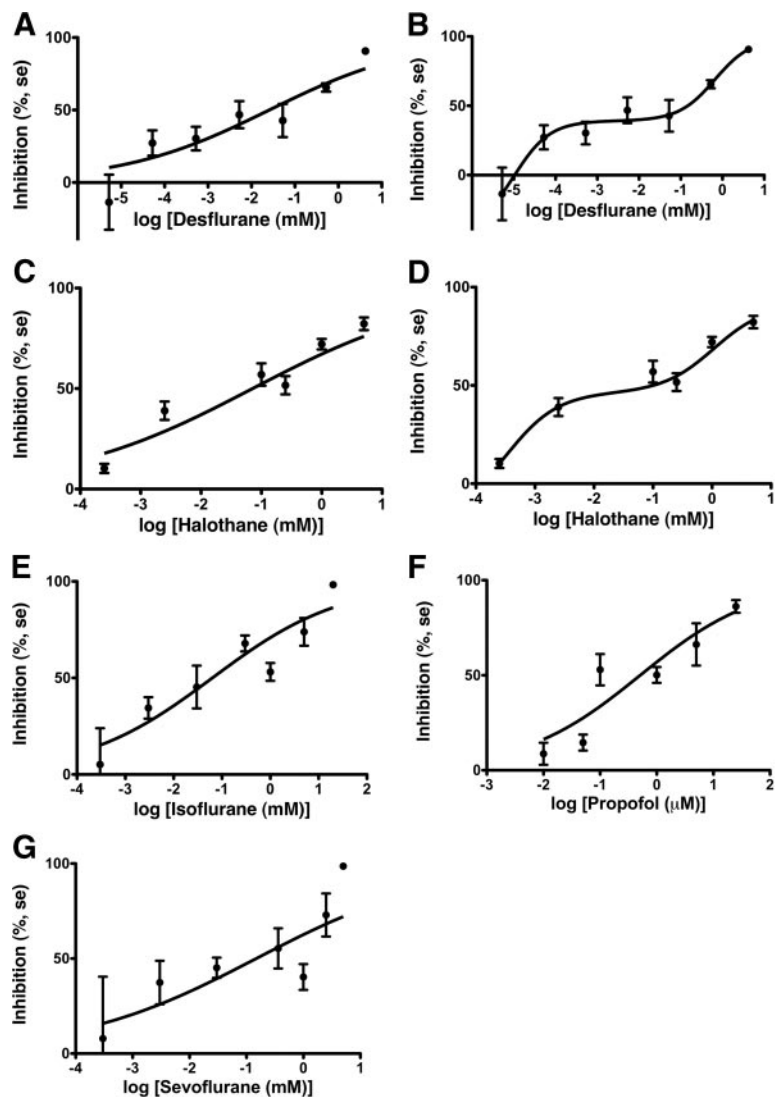


Figure 2. Halogenated inhaled anesthetics and propofol concentration dependently inhibit current through the *Gloeobacter violaceus* ion channel (GLIC). Hill curves are fit to the data in (A), (C), (E), (F), and (G). A total of 40, 39, 41, 31, and 38 oocytes were studied for desflurane, halothane, isoflurane, propofol, and sevoflurane, respectively. The mean change in currents (in percent) and standard errors are displayed at each concentration. For desflurane and halothane, a 2-site model provided a better fit to the data. These are shown in (B) for desflurane and (D) for halothane.

Table 1. IC₅₀ and Hill Coefficients for Modulators of the *Gloeobacter violaceus* Ion Channel (GLIC) and Anesthetizing Concentrations of These Drugs in Animals

| Agent | IC ₅₀ | 95% CI | Hill coefficient | Anesthetic EC ₅₀ |
|----------------------------|------------------|--------------|------------------|-----------------------------|
| Desflurane | 0.03 mM | 0.007–0.1 mM | 0.25 ± 0.05 | 0.56 mM ⁶ |
| Halothane | 0.07 mM | 0.03–0.15 mM | 0.27 ± 0.04 | 0.23 mM ⁶ |
| Isoflurane | 0.06 mM | 0.02–0.2 mM | 0.32 ± 0.07 | 0.28 mM ⁶ |
| Sevoflurane | 0.15 mM | 0.02–1.1 mM | 0.27 ± 0.1 | 0.33 mM ⁶ |
| Propofol | 0.51 μM | 0.21–1.3 μM | 0.42 ± 0.08 | 1.9 μM ⁷ |
| Etomidate | 73 μM | 48–110 μM | 1.1 ± 0.38 | 8.7 μM ⁸ |
| Xenon | 1.05 atm | 0.8–1.38 atm | 1.9 ± 0.47 | 0.71 atm ³ |
| Ethanol ^a | | | | 117–190 mM ⁴ |
| Nitrous oxide ^a | | | | 1.04 atm ⁵ |

IC₅₀ and Hill coefficients are expressed as mean ± SE. Gas phase concentrations are reported for xenon and nitrous oxide and expressed in atmospheres.

CI = confidence interval; IC₅₀ = concentration of anesthetic that produces a 50% change in current; EC₅₀ = 50% effective concentration.

^a Ethanol and nitrous oxide did not modulate GLIC.

halogenated anesthetics and propofol. These compounds modulated GLIC at anesthetic and subanesthetic concentrations (Fig. 2). Hill numbers ranged from 0.25 for desflurane to 0.42 for propofol (Table 1). Xenon and etomidate comprised the second group (Fig. 3). They inhibited agonist-activated currents, but at concentrations at or above anesthetic EC₅₀s, and their concentration-response curves had Hill numbers

of 1. The third group consisted of ethanol and nitrous oxide. These agents did not modulate GLIC at surgical anesthetic concentrations.

Concentration-response curves for anesthetics on receptors from the GABA_A family generally have Hill coefficients of 1 or more.^{10–13} For GLIC, Hill numbers were significantly <1 for desflurane, halothane, isoflurane, sevoflurane, and propofol, an indication of negative

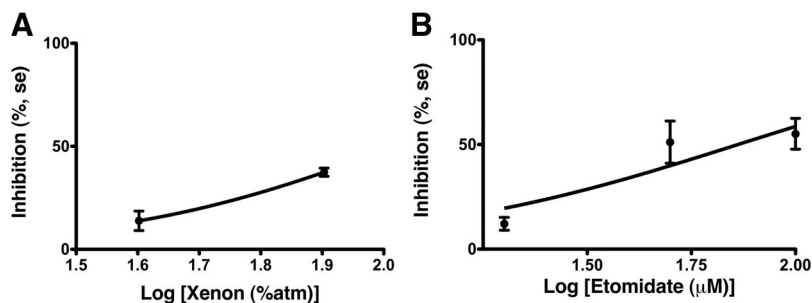


Figure 3. Xenon (A) and etomidate (B) inhibit the *Gloeobacter violaceus* ion channel (GLIC). Nine and 19 oocytes, respectively, were studied. Solid circles denote the mean change in current in percent at each concentration. Error bars display standard errors. Both anesthetics inhibit GLIC.

cooperativity or multiple sites or mechanisms of action. Negative cooperativity can arise when receptor subunits have identical binding sites if binding of 1 ligand decreases the binding affinity of a subsequent ligand. An example is the bacterial homodimeric aspartate receptor, which has identical binding sites for aspartate in the apo (unbound) structure. Only half of these sites are occupied upon ligand binding, with the second site distorted.¹⁴ This contrasts with positive cooperativity, where the doubly liganded state is populated at the expense of the singly liganded state¹⁵ owing to favored binding of a second ligand. Low Hill numbers may also be due to the presence of 2 or more binding sites of different affinity. Photolabeling of multiple tyrosines in nicotinic acetylcholine receptors from *Torpedo californica* with [¹⁴C]halothane shows that >1 anesthetic binding site can be present on a receptor that is homologous to GLIC.¹⁶ Another explanation for anesthetic action over a broad concentration range is that anesthetics interact with GLIC by 2 different mechanisms, such as a binding¹⁷ and a nonbinding mechanism.¹⁸

A 2-site model fit the data better than a 1-site model for halothane and desflurane. Do desflurane and halothane modulate GLIC by a different mechanism than the other halogenated anesthetics and propofol? We note that at approximately the anesthetic EC₅₀, there is a plateau in the inhibitory effect and a small (but in this study, a statistically insignificant) decrease in inhibition for all 4 halogenated anesthetics and propofol (Fig. 2). This is suggestive of a biphasic response of GLIC to these anesthetics, and if it is real, it would also support a model involving 2 sites or mechanisms.

The modulation of GLIC by volatile anesthetics indicates that the volatile anesthetic sensitivity of receptors in the GABA_A superfamily is prokaryotic in origin. This supports the conjecture that the capacity to respond to inhaled anesthetics arose in organisms lacking nervous systems.¹⁹

In summary, GLIC is modulated by many anesthetics. It is unusually sensitive to halogenated anesthetics and propofol compared with other ligand-gated ion channels.^{7,10,13,20–24} These findings, together with the atomic-scale x-ray structure of GLIC, open the door to further structural and functional studies of anesthetic actions on GLIC.

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Sugammadex Provides Faster Reversal of Vecuronium-Induced Neuromuscular Blockade Compared with Neostigmine: A Multicenter, Randomized, Controlled Trial

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BACKGROUND: Sugammadex, a specifically designed γ -cyclodextrin, is a selective relaxant binding drug that rapidly reverses rocuronium-induced and, to a lesser extent, vecuronium-induced neuromuscular blockade. In this study, we compared the efficacy of sugammadex and neostigmine for the reversal of vecuronium-induced neuromuscular blockade in patients scheduled for elective surgery.

METHODS: Patients aged ≥ 18 yr, ASA Class I–III, and scheduled for a surgical procedure under sevoflurane/opioid anesthesia received an intubating dose of vecuronium (0.1 mg/kg) and maintenance doses of 0.02–0.03 mg/kg at reappearance of the second twitch (T_2) of train-of-four (TOF) if required. Neuromuscular blockade was monitored using acceleromyography (TOF-Watch® SX, Schering-Plough Ireland, Dublin, Ireland). At end of surgery, at reappearance of T_2 after the last dose of vecuronium, patients were randomized to receive either sugammadex (2 mg/kg) or neostigmine (50 μ g/kg) plus glycopyrrolate (10 μ g/kg) IV. The primary efficacy end-point was time from start of administration of sugammadex or neostigmine to recovery of TOF ratio to 0.9.

RESULTS: The geometric mean time to recovery of the TOF ratio to 0.9 was significantly faster with sugammadex compared with neostigmine (2.7 min [95% confidence interval {CI}]: 2.2–3.3) versus 17.9 min [95% CI: 13.1–24.3], respectively; $P < 0.0001$). The mean recovery times to a TOF ratio of 0.8 and 0.7 were also significantly shorter with sugammadex. No serious adverse events or unexpected side effects were reported with either drug.

CONCLUSION: Sugammadex provided significantly faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine.

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Although neuromuscular blocking drugs (NMBDs) are used extensively for facilitating surgical procedures and tracheal intubation during anesthesia, concerns have been raised about the risks of postoperative residual neuromuscular blockade, which may be associated with airway obstruction, pulmonary complications, hypoxia, and increased mortality.^{1–3} Rapid and complete reversal of neuromuscular blockade at the end of surgery is therefore mandatory.

Acetylcholinesterase inhibitors, such as neostigmine and edrophonium, are used for the reversal of nondepolarizing neuromuscular blockade, but they

carry a risk of unwanted effects, such as bradycardia, hypotension, bronchoconstriction, hypersalivation, and possibly nausea and vomiting.^{4,5} Anticholinergic drugs, such as atropine or glycopyrrolate, are therefore coadministered to counteract these adverse effects but they may also cause their own side effects, such as tachycardia, blurred vision, sedation, and possibly mild confusion, and should be used with care in the elderly⁶ and in patients with cardiovascular disease. Because of these limitations, there is a need

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The design and conduct of the study, as well as analysis of the study data and opinions, conclusions, and interpretation of the data, were the responsibility of the authors.

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for new reversal drugs with an improved tolerability profile.

Sugammadex, a water-soluble, modified γ -cyclodextrin, is a novel drug developed specifically for the rapid reversal of neuromuscular blockade induced by the steroidal NMBD rocuronium. Sugammadex acts by encapsulating unbound rocuronium and, to a lesser extent, also vecuronium molecules, and reducing the free NMBD fraction at the neuromuscular junction.^{7,8} Studies in surgical patients have demonstrated that sugammadex rapidly and effectively reverses rocuronium-induced neuromuscular blockade.^{9–12} The effects of vecuronium, a compound very similar to rocuronium, can also be reversed by sugammadex.^{11,13,14} However, only few patients¹¹ have received the recommended dose of 2 mg/kg sugammadex after vecuronium so far, and clearly more data are needed for the above combination because this NMBD is (still) used widely around the world.

The present two-armed study was designed to compare the efficacy and side effects of sugammadex versus neostigmine, the current standard reversal drug, for rocuronium- or vecuronium-induced neuromuscular blockade in patients scheduled for elective surgery under sevoflurane anesthesia. Because only insufficient amounts of data are available for sugammadex reversal of rocuronium,* this paper focuses on the vecuronium arm of the study. Sevoflurane anesthesia was chosen because it is an inhaled drug widely used in clinical practice.

The primary objective of this study was to compare recovery from vecuronium-induced neuromuscular blockade with sugammadex to that with neostigmine, and the secondary objective was to evaluate the side effects of a single dose of sugammadex 2 mg/kg or neostigmine 50 μ g/kg (plus glycopyrrolate) in adult patients.

METHODS

Study Design and Patient Selection

This was a multicenter, randomized, active control, safety assessor-blinded trial conducted at 13 sites in Austria, Belgium, Germany, Italy, Spain, Sweden, and the United Kingdom between November 2005 and March 2006. The trial protocol was approved by the Independent Ethics Committee of each center and conducted according to the revised Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable regulatory requirements. The trial has been registered on clinicaltrials.gov (identifier NCT00451217).

Patients were eligible for entry into the trial after giving written informed consent if they were aged

≥ 18 yr, ASA Class I–III, and scheduled for a surgical procedure under general anesthesia in a supine position requiring tracheal intubation. Exclusion criteria included anticipation of a difficult airway, known or suspected neuromuscular disorders, significant renal dysfunction, known or suspected family history of malignant hyperthermia, and allergies to narcotics, muscle relaxants, or other medication used during general anesthesia. Patients receiving medication at a dose and/or timepoint likely to interfere with NMBDs and in whom the use of neostigmine and/or glycopyrrolate could be contraindicated were also excluded, as were those who had already participated in a previous sugammadex trial. Female patients who were pregnant, breast feeding, or of child-bearing age using only hormonal contraception or no means of birth control were also excluded.

Randomization schedules were prepared by Schering-Plough. The randomization codes were entered into a central randomization system that was part of a secured trial website, during the set up of this system. All enrolled patients were allocated a subject number in sequential order of their enrollment into the trial and received a treatment code using the central randomization system.

Study Procedures

An IV cannula was inserted into a vein of the forearm for the administration of anesthetic drugs, vecuronium, and sugammadex or neostigmine. A second IV cannula was inserted into the opposite arm for blood sampling (safety analysis) at predefined timepoints during and after anesthesia. Standard monitoring consisted of electrocardiogram, noninvasive arterial blood pressure measurements, and pulse oximetry, as well as end-tidal CO₂ and sevoflurane measurements.

Anesthesia was induced with an IV opioid (choice was left to the discretion of the investigator) and IV propofol, and maintained using sevoflurane at 1–2 minimum alveolar anesthetic concentration (MAC) end-tidal and opioids, according to each patient's need. After induction of anesthesia but before administration of vecuronium, monitoring of neuromuscular activity was started using acceleromyography (TOF-Watch® SX, Schering-Plough Ireland, Dublin, Ireland) at the adductor pollicis muscle. Repetitive train-of-four (TOF) stimulation was applied at the ulnar nerve at the wrist every 15 s until the end of anesthesia, or at least until recovery of the TOF ratio to 0.9. Stabilization and calibration of the TOF-Watch SX were performed according to good clinical research practice in pharmacodynamic studies of NMBD.¹⁵ During that time (3–10 min) patients' lungs were ventilated via face mask with oxygen/air at normocapnia. Neuromuscular data were collected via a transducer fixed to the top of the thumb using the TOF-Watch SX Monitoring Program. After set-up and stabilization of the TOF-Watch SX, a single bolus dose of IV vecuronium

*Some data from the rocuronium arm of the study have been presented. Blobner M, Eriksson L, Scholz J, Hillebrand H, Pompei L. Sugammadex (2.0 mg/kg) significantly faster reverses shallow rocuronium-induced neuromuscular blockade compared with neostigmine (50 mcg/kg). *Eur J Anaesthesiol* 2007;24(suppl 39):125.

0.1 mg/kg was administered within 10 s into a fast-running infusion, and tracheal intubation was performed after onset of complete blockade. Maintenance doses of vecuronium (0.02–0.03 mg/kg) could be administered as needed at reappearance of the second twitch (T_2) of the TOF (as indicated by the TOF-Watch SX) if clinically required.

At reappearance of T_2 after the last dose of vecuronium, either sugammadex 2 mg/kg (the recommended dose for reversal of shallow vecuronium) or neostigmine 50 $\mu\text{g}/\text{kg}^{16}$ (to a maximum of 5 mg) plus glycopyrrolate 10 $\mu\text{g}/\text{kg}$ were administered in a randomized order as an IV bolus within 10 s. The sevoflurane concentration at the time of reversal was maintained at <1.5 of MAC (0.3–2.8 vol % end-tidal) until recovery of the TOF ratio to 0.9. Sevoflurane was discontinued before tracheal extubation, which was only performed on recovery of the TOF ratio to 0.9. Immediately after tracheal extubation, patients' levels of consciousness were assessed; i.e., whether they were awake and orientated, arousable with minimal stimulation, or responsive only to tactile stimulation. For patients considered cooperative, a 5-s head-lift test and a check for general muscle weakness were performed. These evaluations were repeated every 15 min thereafter until the first head-lift test was achieved. Neuromuscular monitoring was stopped when TOF 0.9 was reached or continued until the end of surgery, depending on the length of the procedure and the preference of the anesthesiologist in charge.

Central body temperature was maintained at $\geq 35^\circ\text{C}$. Heart rate and noninvasive arterial blood pressure measurements were performed continuously and recorded at stable anesthesia, just before administration of vecuronium, at 2, 5, 10, and 30 min after administration of sugammadex or neostigmine and at the postanesthetic visit.

Postanesthetic oxygen saturation and respiratory rate were monitored as part of clinical routine for a minimum of 60 min in the recovery room. Three 10 mL blood samples were collected for safety analysis just before administration of vecuronium, at 4–6 h after administration of sugammadex or neostigmine and at the postanesthetic visit. Urine samples were collected for urinalysis on the day before surgery or just before leaving for the operating room and at the postanesthetic visit, and a physical examination was performed during the 7 days before surgery and at the postanesthetic visit.

Efficacy Variables

The primary efficacy variable was the time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.9. Secondary efficacy variables included the time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, time to recovery of the TOF ratio to 0.8, and assessments of clinical signs of recovery (level of consciousness, 5-s head-lift test, and general

muscle weakness) before transfer to the recovery room after tracheal extubation and before discharge from the recovery room.

Safety Assessments

Safety assessments included pretreatment events (from signing informed consent until administration of sugammadex or neostigmine), serious trial procedure-related events (up to 7 days postdose), and vital signs (heart rate and arterial blood pressure) at screening, prevecuronium, presugammadex, or neostigmine and at 2, 5, 10, and 30 min postdose, and at the postanesthetic visit. Blood samples were assessed for abnormalities in routine biochemistry. Urinalysis included analysis of microalbumin, β_2 -microglobulin, and *N*-acetyl glucosaminidase levels.

Adverse events and serious adverse events were recorded from the time of administration of sugammadex or neostigmine up to 7 days postdose, and any clinically significant changes on physical examination between the first assessment and the postanesthetic assessment were recorded. Clinical signs of possible residual paralysis or reoccurrence of neuromuscular block were also recorded.

Statistics

Efficacy analyses were performed using data from the intent-to-treat (ITT) population, which consisted of all randomized subjects who received sugammadex or neostigmine and had at least one efficacy measurement. Time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9 was analyzed using a two-way analysis of variance model in which treatment group and trial site were the factors of the model. Because it was expected that the variance of recovery times after administration of sugammadex and neostigmine would differ, the analysis of variance was applied to logarithm-transformed recovery times.^{17,18} Two-sided statistical testing was done at a significance level of 5%.

A separate analysis was also performed in which missing recovery times were imputed using a conservative approach toward sugammadex. It was considered conservative because relatively long recovery times were imputed for sugammadex subjects with missing recovery times and relatively short recovery times were imputed for neostigmine subjects (Appendix).

Because the recovery times in both groups followed a skewed distribution, and because large observations have a major influence on the arithmetic mean, this summary measure is prone to sampling error.¹⁹ However, the geometric mean is robust against large observations arising from data with skewed distribution and was warranted in the current study.¹⁹ Therefore, the

†When data are log-transformed and statistically analyzed in this way, the *P* values obtained in the analysis are related to comparison of the two geometric means, answering the question: is the ratio of the two geometric means different from one (alternative hypothesis) or not (null hypothesis)?

recovery times from administration of sugammadex or neostigmine to a TOF ratio of 0.7, 0.8, or 0.9 were summarized using the geometric mean (calculated by taking the logarithm of each subject's recovery time to TOF 0.7, 0.8, or 0.9, then calculating the arithmetic mean of the logarithm-transformed data, and finally transforming back into the original time scale by taking the antilogarithm). Data were also summarized using median and range values.

RESULTS

Baseline Characteristics

One hundred patients were enrolled in the study, of which 51 were randomized to the sugammadex group and 49 to the neostigmine group. Three subjects in the sugammadex group and four in the neostigmine group did not receive the study drug. Reasons for discontinuation in the sugammadex group were refusal of surgical procedure ($n = 1$) and TOF-Watch SX problems ($n = 2$). In the neostigmine group, patients were discontinued because of unavailability of site staff to perform the protocol ($n = 1$), randomization failure ($n = 1$), surgeon's withdrawal of consent for operating room time for the research team ($n = 1$), and a TOF-Watch SX problem ($n = 1$). Hence, 48 subjects in the sugammadex group and 45 in the neostigmine group were treated (representing the all-subjects-treated population). All treated patients had at least one efficacy measurement and therefore the all-subjects-treated population was equivalent to the ITT population. The treatment groups had similar baseline characteristics (Table 1).

Efficacy

In the ITT population, the time from start of administration of study drug to recovery of the TOF ratio to 0.9 was estimated to be 6.6 times faster with sugammadex compared with neostigmine (95% confidence interval [CI]: 4.7–9.3). Geometric mean times (95% CI) to recovery of the TOF ratio to 0.9 were 2.7 (2.2–3.3) min after sugammadex and 17.9 (13.1–24.3) min after neostigmine ($P < 0.0001$) (Table 2). The 95th percentile of the time to recovery of the TOF ratio to 0.9 was 6.95 min in the sugammadex group and 76.15 min in the neostigmine group.

In addition, the mean times to recovery of the TOF ratio to 0.7 and 0.8 were also significantly faster with sugammadex compared with neostigmine (Table 2). The 95th percentile of the time to recovery of the TOF ratio to 0.8 was 3.7 min in the sugammadex group and 41.4 min in the neostigmine group. A comparison of results for this dataset (termed the completed cases dataset), which includes only those patients providing times to TOF ratios of 0.9, 0.8, or 0.7, was made with results for an imputed data analysis dataset (times to TOF 0.9, 0.8, or 0.7 were imputed for those patients with missing values) and shows virtually no difference between the two approaches (Table 3).

Table 1. Baseline Characteristics (All-Subjects-Treated Population)

| | Sugammadex ($n = 48$) | Neostigmine ($n = 45$) |
|------------------------|----------------------------|-----------------------------|
| Age (yr), mean (SD) | 49 (16) | 50 (15) |
| Weight (kg), mean (SD) | 81 (19) | 76 (13) |
| Height (cm), mean (SD) | 173 (11) | 170 (11) |
| Gender (M/F), n (%) | 26/22 (54/46) | 21/24 (47/53) |
| ASA Class, n (%) | | |
| I | 18 (38) | 17 (38) |
| II | 27 (56) | 25 (56) |
| III | 3 (6) | 3 (7) |

Figure 1 shows the neuromuscular recovery profile for two patients after administration of sugammadex and neostigmine. Figure 2 shows the percentage of patients who had achieved a TOF ratio of 0.9 over the course of the study. In the sugammadex group, monitoring was stopped in a median (range) of 17 (1–105) min after TOF >0.9 was attained, and 13 patients (28%) were monitored for >30 min. In the neostigmine group, the TOF recordings were stopped in a median (range) of 5 (1–177) min (five subjects [11%] for >30 min) after the last TOF evaluation. Eight patients in the neostigmine group failed to achieve a TOF ratio of 0.9 during the monitoring period. Three other neostigmine patients and two sugammadex patients are not included in Figure 2 because the time to a TOF ratio of 0.9 was not available (neuromuscular monitoring was stopped prematurely 30 min after administration of study drug in one patient in the neostigmine group) or considered unreliable ($n = 2$ in both groups). Two patients receiving sugammadex had unexpectedly long recovery times to a TOF ratio of 0.9 (20 and 64 min) but were within the normal range for time to recovery to a TOF ratio of 0.8 (4.3 and 3.7 min, respectively). Before and after reversal, the sevoflurane concentrations were similar between the two groups.

Of those subjects randomized to receive sugammadex for reversal of vecuronium-induced neuromuscular blockade, and who provided evaluable data for the time to recovery to TOF 0.9 ($n = 46$), 27 received only an intubating dose and 19 received an intubating dose plus one or more maintenance doses (range, 1–15 maintenance doses). Of the evaluable patients in the neostigmine group ($n = 34$), 27 patients received only an intubating dose of vecuronium and 7 received one or more maintenance doses (range, 1–4 maintenance doses). Geometric mean time to recovery of the TOF ratio to 0.9 after administration of sugammadex was slightly shorter in patients who received an intubating dose of vecuronium only, compared with those who received at least one maintenance dose of vecuronium, whereas recovery of the TOF ratio to 0.9 after neostigmine was considerably shorter in those who received an intubating dose only (Table 4). As no comparison of the recovery times after maintenance doses was planned in the protocol, only descriptive information can be given in the above-mentioned table.

Table 2. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of-Four (TOF) Ratio to 0.9, 0.8, and 0.7 (Intent-to-Treat Population)

| | Sugammadex | Neostigmine | P |
|------------------------------|-----------------|-----------------|----------|
| Recovery of TOF ratio to 0.9 | | | |
| N | 46 ^a | 34 ^b | < 0.0001 |
| Geometric mean | 2.7 | 17.9 | |
| Median (range) | 2.1 (1.2–64.2) | 21.9 (2.9–76.2) | |
| Recovery of TOF ratio to 0.8 | | | |
| N | 46 ^a | 42 ^c | < 0.0001 |
| Geometric mean | 1.9 | 10.8 | |
| Median (range) | 1.7 (1.0–4.3) | 13.6 (2.2–59.1) | |
| Recovery of TOF ratio to 0.7 | | | |
| N | 46 ^a | 43 ^d | < 0.0001 |
| Geometric mean | 1.6 | 6.4 | |
| Median (range) | 1.4 (0.7–3.4) | 5.2 (1.9–54.3) | |

^a Data excluded from two patients as TOF data to 0.9, 0.8, and 0.7 were considered unreliable because of unstable TOF baseline.

^b Data excluded from 11 patients because TOF data to 0.9 were missing (8 patients failed to achieve a TOF ratio of 0.9, 1 patient did not have a recovery time measured for TOF to 0.9, and in 2 patients the TOF data to 0.9 were considered unreliable because of unstable TOF baseline).

^c Data excluded from three patients as TOF data to 0.8 were either missing (two patients) or considered unreliable because of unstable TOF baseline (one patient).

^d Data excluded from two patients as TOF data to 0.7 were either missing (one patient) or considered unreliable because of unstable TOF baseline (one patient).

Table 3. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of-Four (TOF) Ratio to 0.9, 0.8, and 0.7 in Completed Cases and Imputed Data (Intent-to-Treat Population)

| Recovery of TOF ratio to | Analysis using | Sugammadex Geometric mean | Neostigmine Geometric mean | Estimated treatment effect ^a (95% CI) |
|--------------------------|-----------------|---------------------------|----------------------------|--|
| 0.9 | Completed cases | 2.7 (n = 46) | 17.9 (n = 34) | 6.6 (4.7, 9.3) |
| | Imputed data | 2.8 (n = 48) | 16.8 (n = 45) | 6.7 (5.0, 9.1) |
| 0.8 | Completed cases | 1.9 (n = 46) | 10.8 (n = 42) | 5.9 (4.4, 8.0) |
| | Imputed data | 2.0 (n = 48) | 10.2 (n = 45) | 5.4 (4.0, 7.2) |
| 0.7 | Completed cases | 1.6 (n = 46) | 6.4 (n = 43) | 4.2 (3.1, 5.6) |
| | Imputed data | 1.6 (n = 48) | 6.1 (n = 45) | 3.9 (2.9, 5.2) |

CI = confidence interval.

^a Treatment effect is defined here as the ratio of the geometric mean recovery time after neostigmine over the geometric mean recovery time after sugammadex. Estimate for treatment effect is obtained from analysis of variance on log-transformed data.

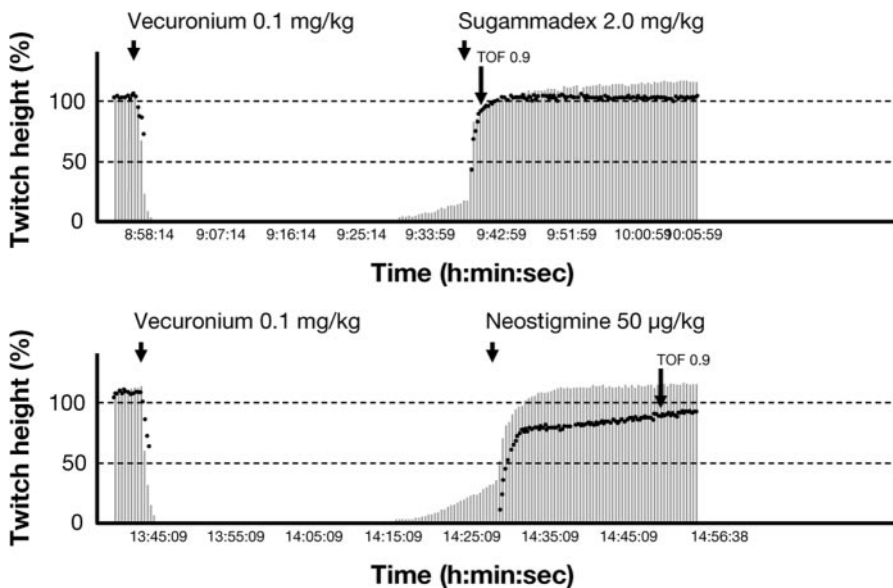


Figure 1. Examples of recovery profiles for vecuronium 0.1 mg/kg after administration of sugammadex 2.0 mg/kg or neostigmine 50 µg/kg at reappearance of second twitch (T_2). Bars represent first twitch (T_1) values (twitch height %) and dots the train-of-four (TOF [T_4/T_1]) ratio. TOF 0.9 arrow represents the time to attain a TOF ratio of 0.9 after administration of sugammadex and neostigmine, $P < 0.0001$ (for the difference between the geometric means for the two groups).

In terms of clinical signs of recovery, 29 of 48 patients (60.4%) in the sugammadex group and 26 of 45 patients (57.8%) in the neostigmine group were awake and oriented before transfer to the recovery room, and all except 7 patients in each group were cooperative. Only one patient in the sugammadex

group and six in the neostigmine group were unable to perform the 5-s head lift before transfer to the recovery room, and general muscle weakness was reported in four and six patients in each group, respectively. Before discharge from the recovery room, the clinical signs of recovery were similar in

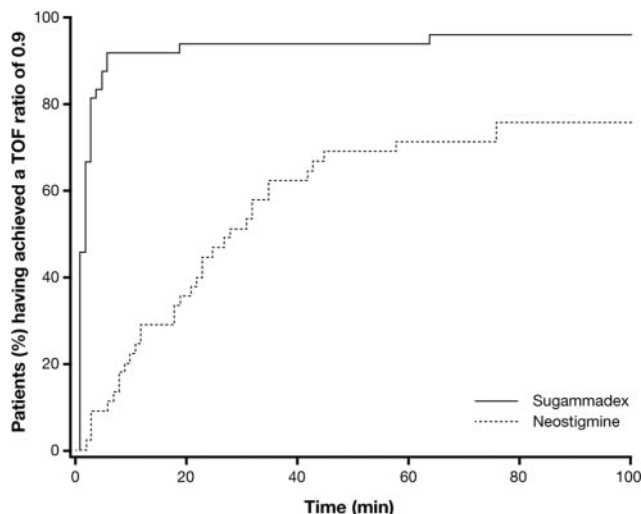


Figure 2. Percentage of patients having achieved a train-of-four (TOF) ratio to 0.9 after reversal of vecuronium-induced neuromuscular blockade with sugammadex or neostigmine (intent-to-treat population). Patients with missing data are not included. Time to TOF ratio of 0.9 = the time from start of administration of sugammadex or neostigmine to TOF ratio of 0.9.

both groups. Except for one subject in the neostigmine group, who was arousable with minimal stimulation, all patients were awake and oriented, cooperative, and able to perform the 5-s head lift, and none had general muscle weakness.

Safety

There were no serious adverse events or serious trial procedure-related events in this study. No patients discontinued from the trial because of an adverse event. Seventeen patients experienced one or more adverse events that were considered by the investigator to be possibly, probably, or definitely related to study drug: 7 (14.6%) in the sugammadex group and 10 (22.2%) in the neostigmine group.

Drug-related adverse events occurring in each group are summarized in Table 5. All of these were mild or moderate in nature except for two events in the neostigmine group that were classified by the investigator as severe: one case of prolonged neuromuscular blockade and one sleeping disorder. None of

the drug-related events was reported as a serious adverse event.

Overall, there were no marked differences in routine laboratory variables between the sugammadex and neostigmine groups.

Mean values for systolic and diastolic blood pressure and heart rate from the screening visit to the postanesthetic visit were similar in both treatment groups. Higher mean diastolic blood pressure at 2 min postdose with neostigmine (64 vs 59 mm Hg) and a faster heart rate with neostigmine at 2 min (74 vs 61 bpm) and 5 min postdose (70 vs 62 bpm) compared with sugammadex were observed (Figs. 3 and 4). Central body temperature was maintained at $\geq 35^{\circ}\text{C}$ in all patients except one in the neostigmine group and two in the sugammadex group. As the temperature deviations were only minor and for short periods, these were not considered to have an effect on recovery in these patients.

There was no clinical evidence of reoccurrence of neuromuscular block or residual neuromuscular blockade in either group.

DISCUSSION

The results of this randomized, actively controlled study demonstrate that sugammadex achieves reversal of vecuronium-induced neuromuscular blockade significantly more rapidly than neostigmine. The (geometric) mean times to achieve a TOF ratio of 0.9 with sugammadex and neostigmine were 2.7 and 17.9 min, respectively, resulting in a reversal time that was almost seven times faster with sugammadex compared with neostigmine.

The results presented are for completed cases only; that is, patients for whom recovery times to the respective TOF ratio of 0.7, 0.8, or 0.9 were available. Another analysis was also done in which missing recovery times were imputed using a conservative approach for sugammadex and a best-case scenario for neostigmine. There was no statistical difference between the completed cases analysis reported here and the imputed data analysis.

The geometric mean time to reversal of neuromuscular blockade (TOF of 0.9) with sugammadex 2.0

Table 4. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of Four (TOF) Ratio to 0.9 for Patients Who Received an Intubating Dose Only and Those Who Received at Least One Maintenance Dose of Vecuronium (Exploratory Analysis of the Intent-to-Treat Population)

| | Sugammadex group | | Neostigmine group | |
|------------------------------|----------------------|--------------------------------------|----------------------|--------------------------------------|
| | Intubating dose only | Intubating dose and maintenance dose | Intubating dose only | Intubating dose and maintenance dose |
| Recovery of TOF ratio to 0.9 | | | | |
| N | 27 ^a | 19 ^a | 27 ^b | 7 ^b |
| Geometric mean | 2.3 | 3.5 | 15.9 | 28.0 |
| Median (range) | 1.9 (1.2–64.2) | 3.4 (1.7–19.8) | 18.9 (2.9–76.2) | 35.7 (6.2–76.2) |

^a Data excluded from one patient in each group of the sugammadex cohort ($n = 48$) because TOF data to 0.9 were considered unreliable.

^b Data excluded from five patients in the intubating dose only group and six patients in the intubating plus maintenance doses group of the neostigmine cohort ($n = 45$) either because the time to recovery data were unavailable or because the TOF data to 0.9 were considered unreliable.

Table 5. Incidence (Number [%] of Patients) of Drug-Related^a Adverse Events (All-Subjects-Treated Population)

| | Sugammadex (n = 48) | Neostigmine (n = 45) |
|--|------------------------|-------------------------|
| Chills | 2 (4.2) | 0 (0) |
| Nausea | 2 (4.2) | 2 (4.4) |
| Procedural hypertension | 2 (4.2) | 1 (2.2) |
| Vomiting | 2 (4.2) | 0 (0) |
| Vertigo | 1 (2.1) | 0 (0) |
| Headache | 1 (2.1) | 0 (0) |
| Retching | 1 (2.1) | 0 (0) |
| Airway complication of anesthesia | 1 (2.1) | 0 (0) |
| Postprocedural nausea | 1 (2.1) | 0 (0) |
| Hot flush | 1 (2.1) | 0 (0) |
| Body temperature increased | 1 (2.1) | 0 (0) |
| Procedural complication (i.e., increased/decreased heart rate) | 0 (0) | 4 (8.9) |
| Dry mouth | 0 (0) | 4 (8.9) |
| Neuromuscular blockade prolonged | 0 (0) | 2 (4.4) |
| Supraventricular extrasystoles | 0 (0) | 1 (2.2) |
| Ventricular extrasystoles | 0 (0) | 1 (2.2) |
| Sleep disorder | 0 (0) | 1 (2.2) |
| Erythema | 0 (0) | 1 (2.2) |
| γ-Glutamyltransferase increased | 0 (0) | 1 (2.2) |
| Heart rate increased | 0 (0) | 1 (2.2) |

^a Considered by the investigator to be possibly, probably, or definitely related to study drug.

mg/kg in this study was in line with the results observed previously in a dose-finding study, in which sugammadex 2.0 mg/kg administered at reappearance of T_2 was found to reverse neuromuscular blockade at a mean time of 2.3 min, after administration of the same dose of vecuronium (0.1 mg/kg) under anesthesia with a target-controlled infusion of propofol.¹¹ These results suggest that after vecuronium-induced neuromuscular blockade time to recovery from sugammadex administration to a TOF ratio of 0.9 is in the range of 2–3 min. In comparison, even faster recovery times, in the range of 1–2 min, have been observed for reversal of rocuronium-induced blockade with sugammadex.^{9–12}

Recovery to a TOF ratio of at least 0.9 is now considered to be the “gold standard” for neuromuscular recovery after administration of NMBD.^{15,19,20} For this reason, time to achieve a TOF ratio of 0.9 was selected as the primary efficacy end-point in this study. Although the use of acceleromyography is more prone to artifacts than mechanomyography, it is widely accepted for research.¹⁵ As it is easier to use in the clinical setting, neuromuscular monitoring was performed with acceleromyography in this study, in accordance with previous sugammadex trials.

Neostigmine should only be administered when some signs of recovery from neuromuscular block occur^{15,16} and therefore reappearance of T_2 (measured by the TOF-Watch SX) was chosen. This approach might

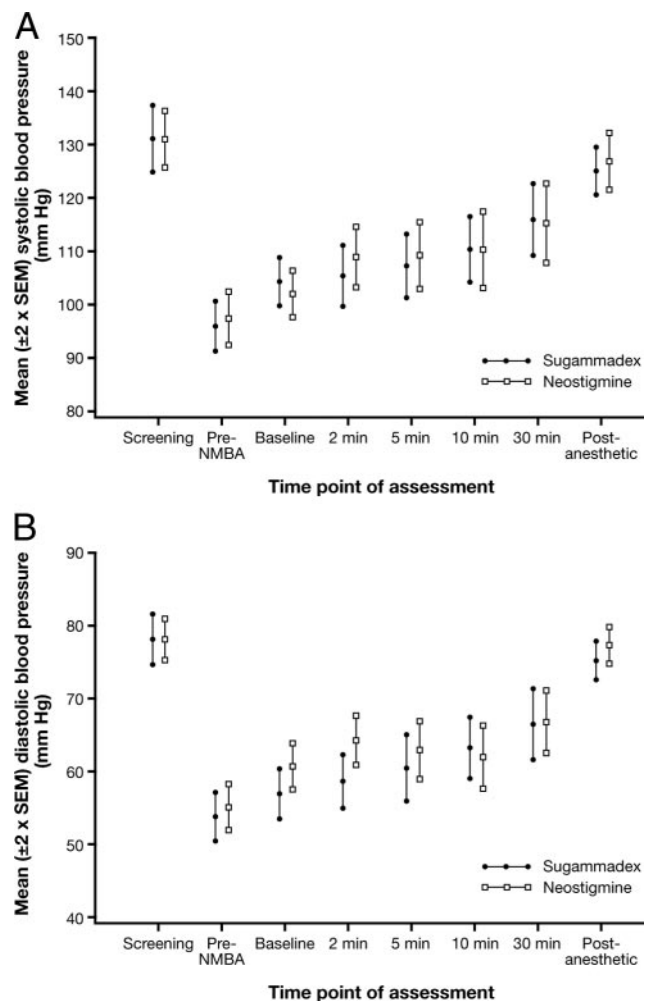


Figure 3. Mean systolic (A) and diastolic (B) blood pressure rate before (at screening, preneuromuscular blocking agent [NMBA], and baseline) and after administration (at timepoints shown) of sugammadex or neostigmine (all-subjects-treated population). SEM = standard error of the mean.

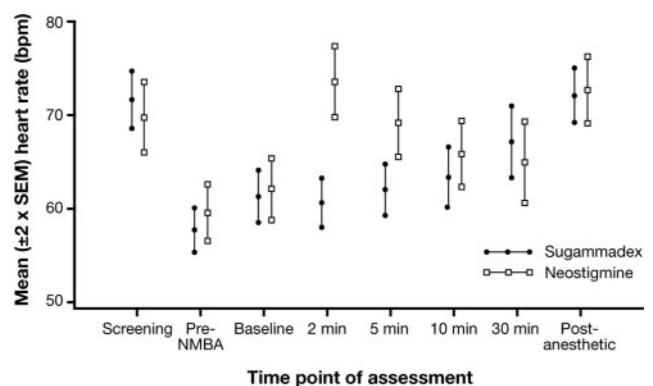


Figure 4. Mean heart rate before (at screening, preneuromuscular blocking agent [NMBA], and baseline) and after administration (at timepoints shown) of sugammadex or neostigmine (all-subjects-treated population). SEM = standard error of the mean.

enable transfer of the data obtained in this study into clinical practice. Many clinicians unfortunately still only use a peripheral nerve stimulator for monitoring of neuromuscular function and reappearance of the T_2 can

also be determined with nonquantitative monitoring devices.

Residual neuromuscular blockade may be observed in patients in the recovery room after surgery and has been shown to be associated with significant morbidity.^{1,3,21,22} In one study, residual blockade defined as a TOF ratio <0.9 was reported on arrival in the recovery room in 45% of patients administered a single intubating dose of an intermediate acting NMBD without reversal, and 16% of patients had a TOF ratio as low as <0.7 .²² There was no clinical evidence of residual neuromuscular blockade in our study after reversal with either sugammadex or neostigmine. Eight patients in the neostigmine group failed to achieve a TOF of ≥ 0.9 ; sevoflurane was discontinued in these patients either because recovery took too long or surgery was finished and tracheal extubation was performed before a TOF ratio of 0.9 (and occasionally 0.8) was reached. This prolonged recovery and early tracheal extubation may be associated with a possible risk of residual paralysis. However, even after early reversal of high-dose rocuronium (1.2 mg/kg) with sugammadex, adequate TOF values were sustained,²³ with no evidence of reparable paralysis. Failure to achieve a TOF of ≥ 0.9 in some neostigmine patients in the current study may have been related to the use of sevoflurane, which has been shown to enhance the effect of NMBDs²⁴ and to delay reversal of neuromuscular blockade with neostigmine.²⁵ In contrast, all patients in the sugammadex group achieved a TOF of ≥ 0.9 , although two patients did have unexpectedly long recovery times (20 and 64 min). A possible effect of hypothermia could be excluded because central core temperature and skin temperature above the thenar muscle remained above 35°C and 33°C, respectively. Whether this was a prolonged recovery from neuromuscular blockade or the effect of sevoflurane is unknown. Both patients recovered clinically. Previous results suggest that sevoflurane does not have an effect on the action of sugammadex when administered for reversal at T_2 .¹² For one of the patients with outlying recovery times, time to achieve a TOF of ≥ 0.9 on three consecutive TOF stimulations was prolonged, although the TOF ratio returned to 0.7 and 0.8 after 2.2 and 3.7 min, respectively. TOF recovery was defined by the first of three consecutive TOF values. The first TOF ≥ 0.9 was reached at 8.7 min; the curve then varied between TOF 0.79 and 0.93 with three consecutive TOF values of ≥ 0.9 being reached after only 64 min. For the other patient, the TOF ratio returned to 0.7 and 0.8 after 2.3 and 4.3 min, respectively, but a plateau TOF ratio of 0.85–0.87 was observed for 10 min. Thus, the 95th percentile of the time to recovery of the TOF ratio to 0.8 was only 3.7 min in the sugammadex group, much shorter than the 95th percentile of the time to recovery of the TOF ratio to 0.9 of 6.95 min. In contrast, the 95th percentile of the time to recovery of the TOF ratio to 0.8 was 41.4 min in the neostigmine group. Although

the use of sevoflurane may have influenced the recovery time as it enhances the effect of NMBDs, it was selected because it is an inhaled drug frequently used in clinical practice. Sevoflurane concentrations administered during recovery were in the same range (and always below 1.5 MAC) in both groups.

Table 4 shows that the geometric mean recovery time to TOF ratio of 0.9 for patients who received an intubating dose of vecuronium is only slightly shorter compared with patients who also received one or more maintenance doses. Because of the small number of patients who received maintenance doses, no statistical analysis was planned or performed. There was no apparent correlation between recovery time and number of maintenance doses administered. The only patient who received 15 maintenance doses of vecuronium followed by sugammadex recovered in 1.7 min, one of the fastest recovery times in the sugammadex group. Also, in the case of neostigmine, the recovery time to TOF ratio of 0.9 did not increase with an increasing number of maintenance doses.

The incidence and profile of drug-related adverse events was generally low and similar in the sugammadex and neostigmine groups, and there were no reports of serious adverse events. Overall, the incidence of drug-related adverse events was slightly higher in the neostigmine group compared with the sugammadex group (22.2% vs 14.6% of patients), and this was largely accounted for by a higher incidence of dry mouth (four cases) and procedural complications of mild-to-moderate intensity (one case of bradycardia and three cases of increased heart rate). The similar tolerability profile of sugammadex and neostigmine reported in this study was unexpected given the fact that, in contrast to neostigmine, sugammadex does not affect cholinergic transmission and is therefore unlikely to cause cholinergic side effects.²⁶ However, it should be noted that this study was not specifically designed to evaluate any differences between sugammadex and neostigmine in terms of cardiovascular or other side effects and therefore no comparative statistics were applied here.

Evaluation of changes in vital signs during the study do suggest, however, that sugammadex may be associated with fewer hemodynamic effects compared with neostigmine. Although the course for mean systolic blood pressure was similar in both groups, the increase in mean diastolic blood pressure at 2 min postdose was higher with neostigmine compared with sugammadex, as was the increase in mean heart rate at 2 and 5 min postdose.

In conclusion, the results of this study show that under sevoflurane anesthesia sugammadex is significantly more effective than neostigmine for recovery from neuromuscular blockade induced by vecuronium.

APPENDIX

Method for Imputation of Missing Recovery Times

In cases where times from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9 were missing, values were imputed using a conservative approach for sugammadex. Thus, relatively long recovery times were imputed for sugammadex subjects and relatively short recovery times were imputed for neostigmine subjects with missing recovery times.

Cases Where Times to TOF Ratio of 0.9 were Missing

If the time to recovery of the TOF ratio of 0.8 was available, then imputation of the time to a TOF ratio of 0.9 was performed as follows:

- Sugammadex group: for all subjects who were randomized to receive sugammadex and had times to recovery of the TOF ratio to 0.8 and 0.9, the difference between these two recovery times was determined. The 95th percentile (representing a long time interval for recovery from TOF 0.8 to 0.9) of these differences was calculated and then added to the time to recovery of the TOF ratio to 0.8.
- Neostigmine group: the same procedure as for sugammadex subjects with missing times was performed but only subjects randomized to receive neostigmine were used, the 5th percentile (representing a short time interval for recovery from TOF 0.8 to 0.9) of the differences in time to recovery of the TOF ratio to 0.8 and 0.9 was calculated, and added to the time to recovery of the TOF ratio to 0.8.
- If, for a given subject, the times from the start of administration of study drug to recovery of the TOF ratio to 0.8 were also missing but the time to the TOF ratio of 0.7 was available, then imputation of the time to a TOF ratio of 0.9 was performed as follows:
- Sugammadex group: for all subjects who were randomized to sugammadex and had times to recovery of the TOF ratio to 0.7 and 0.9 available, the difference between these two recovery times was determined. The 95th percentile of these differences was calculated and then added to the time to recovery of the TOF ratio to 0.7.
- Neostigmine group: the same procedure as for sugammadex subjects was performed, but only subjects randomized to receive neostigmine were used, the 5th percentile of the differences in time to recovery of the TOF ratio to 0.7 and 0.9 was calculated, and added to the time to recovery of the TOF ratio to 0.7.
- For all sugammadex-treated patients where the times to recovery of the TOF ratio to 0.9, 0.8, and 0.7 were unavailable, the imputed time for recovery to a TOF ratio of 0.9 was the 95th percentile of

the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive sugammadex. Similarly, for all neostigmine-treated patients where the time to recovery of the TOF ratio to 0.9, 0.8, and 0.7 was unavailable, the imputed time for recovery to a TOF ratio of 0.9 was the 5th percentile of the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive neostigmine.

Cases Where Times to TOF Ratio of 0.8 were Missing

Imputation of missing times from the start of administration of study drug to recovery of the TOF ratio to 0.8 followed a corresponding procedure to that used for missing times to a TOF ratio of 0.9: the 95th percentile (sugammadex) or 5th percentile (neostigmine) of the differences in time between recovery of the TOF ratio to 0.7 and 0.8 was used.

Cases Where Times to TOF Ratio of 0.7 were Missing

The 95th percentile observed time for subjects randomized to sugammadex and 5th percentile observed time for subjects randomized to neostigmine were imputed for subjects in whom the time to recovery of the TOF ratio to 0.7 was unavailable.

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Sugammadex Provides Faster Reversal of Vecuronium-Induced Neuromuscular Blockade Compared with Neostigmine: A Multicenter, Randomized, Controlled Trial

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BACKGROUND: Sugammadex, a specifically designed γ -cyclodextrin, is a selective relaxant binding drug that rapidly reverses rocuronium-induced and, to a lesser extent, vecuronium-induced neuromuscular blockade. In this study, we compared the efficacy of sugammadex and neostigmine for the reversal of vecuronium-induced neuromuscular blockade in patients scheduled for elective surgery.

METHODS: Patients aged ≥ 18 yr, ASA Class I–III, and scheduled for a surgical procedure under sevoflurane/opioid anesthesia received an intubating dose of vecuronium (0.1 mg/kg) and maintenance doses of 0.02–0.03 mg/kg at reappearance of the second twitch (T_2) of train-of-four (TOF) if required. Neuromuscular blockade was monitored using acceleromyography (TOF-Watch® SX, Schering-Plough Ireland, Dublin, Ireland). At end of surgery, at reappearance of T_2 after the last dose of vecuronium, patients were randomized to receive either sugammadex (2 mg/kg) or neostigmine (50 μ g/kg) plus glycopyrrolate (10 μ g/kg) IV. The primary efficacy end-point was time from start of administration of sugammadex or neostigmine to recovery of TOF ratio to 0.9.

RESULTS: The geometric mean time to recovery of the TOF ratio to 0.9 was significantly faster with sugammadex compared with neostigmine (2.7 min [95% confidence interval {CI}]: 2.2–3.3) versus 17.9 min [95% CI: 13.1–24.3], respectively; $P < 0.0001$). The mean recovery times to a TOF ratio of 0.8 and 0.7 were also significantly shorter with sugammadex. No serious adverse events or unexpected side effects were reported with either drug.

CONCLUSION: Sugammadex provided significantly faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine.

(Anesth Analg 2010;110:64–73)

Although neuromuscular blocking drugs (NMBDs) are used extensively for facilitating surgical procedures and tracheal intubation during anesthesia, concerns have been raised about the risks of postoperative residual neuromuscular blockade, which may be associated with airway obstruction, pulmonary complications, hypoxia, and increased mortality.^{1–3} Rapid and complete reversal of neuromuscular blockade at the end of surgery is therefore mandatory.

Acetylcholinesterase inhibitors, such as neostigmine and edrophonium, are used for the reversal of nondepolarizing neuromuscular blockade, but they

carry a risk of unwanted effects, such as bradycardia, hypotension, bronchoconstriction, hypersalivation, and possibly nausea and vomiting.^{4,5} Anticholinergic drugs, such as atropine or glycopyrrolate, are therefore coadministered to counteract these adverse effects but they may also cause their own side effects, such as tachycardia, blurred vision, sedation, and possibly mild confusion, and should be used with care in the elderly⁶ and in patients with cardiovascular disease. Because of these limitations, there is a need

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The design and conduct of the study, as well as analysis of the study data and opinions, conclusions, and interpretation of the data, were the responsibility of the authors.

Reprints will not be available from the author.

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for new reversal drugs with an improved tolerability profile.

Sugammadex, a water-soluble, modified γ -cyclodextrin, is a novel drug developed specifically for the rapid reversal of neuromuscular blockade induced by the steroidal NMBD rocuronium. Sugammadex acts by encapsulating unbound rocuronium and, to a lesser extent, also vecuronium molecules, and reducing the free NMBD fraction at the neuromuscular junction.^{7,8} Studies in surgical patients have demonstrated that sugammadex rapidly and effectively reverses rocuronium-induced neuromuscular blockade.^{9–12} The effects of vecuronium, a compound very similar to rocuronium, can also be reversed by sugammadex.^{11,13,14} However, only few patients¹¹ have received the recommended dose of 2 mg/kg sugammadex after vecuronium so far, and clearly more data are needed for the above combination because this NMBD is (still) used widely around the world.

The present two-armed study was designed to compare the efficacy and side effects of sugammadex versus neostigmine, the current standard reversal drug, for rocuronium- or vecuronium-induced neuromuscular blockade in patients scheduled for elective surgery under sevoflurane anesthesia. Because only insufficient amounts of data are available for sugammadex reversal of rocuronium,* this paper focuses on the vecuronium arm of the study. Sevoflurane anesthesia was chosen because it is an inhaled drug widely used in clinical practice.

The primary objective of this study was to compare recovery from vecuronium-induced neuromuscular blockade with sugammadex to that with neostigmine, and the secondary objective was to evaluate the side effects of a single dose of sugammadex 2 mg/kg or neostigmine 50 μ g/kg (plus glycopyrrolate) in adult patients.

METHODS

Study Design and Patient Selection

This was a multicenter, randomized, active control, safety assessor-blinded trial conducted at 13 sites in Austria, Belgium, Germany, Italy, Spain, Sweden, and the United Kingdom between November 2005 and March 2006. The trial protocol was approved by the Independent Ethics Committee of each center and conducted according to the revised Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable regulatory requirements. The trial has been registered on clinicaltrials.gov (identifier NCT00451217).

Patients were eligible for entry into the trial after giving written informed consent if they were aged

≥ 18 yr, ASA Class I–III, and scheduled for a surgical procedure under general anesthesia in a supine position requiring tracheal intubation. Exclusion criteria included anticipation of a difficult airway, known or suspected neuromuscular disorders, significant renal dysfunction, known or suspected family history of malignant hyperthermia, and allergies to narcotics, muscle relaxants, or other medication used during general anesthesia. Patients receiving medication at a dose and/or timepoint likely to interfere with NMBDs and in whom the use of neostigmine and/or glycopyrrolate could be contraindicated were also excluded, as were those who had already participated in a previous sugammadex trial. Female patients who were pregnant, breast feeding, or of child-bearing age using only hormonal contraception or no means of birth control were also excluded.

Randomization schedules were prepared by Schering-Plough. The randomization codes were entered into a central randomization system that was part of a secured trial website, during the set up of this system. All enrolled patients were allocated a subject number in sequential order of their enrollment into the trial and received a treatment code using the central randomization system.

Study Procedures

An IV cannula was inserted into a vein of the forearm for the administration of anesthetic drugs, vecuronium, and sugammadex or neostigmine. A second IV cannula was inserted into the opposite arm for blood sampling (safety analysis) at predefined timepoints during and after anesthesia. Standard monitoring consisted of electrocardiogram, noninvasive arterial blood pressure measurements, and pulse oximetry, as well as end-tidal CO₂ and sevoflurane measurements.

Anesthesia was induced with an IV opioid (choice was left to the discretion of the investigator) and IV propofol, and maintained using sevoflurane at 1–2 minimum alveolar anesthetic concentration (MAC) end-tidal and opioids, according to each patient's need. After induction of anesthesia but before administration of vecuronium, monitoring of neuromuscular activity was started using acceleromyography (TOF-Watch® SX, Schering-Plough Ireland, Dublin, Ireland) at the adductor pollicis muscle. Repetitive train-of-four (TOF) stimulation was applied at the ulnar nerve at the wrist every 15 s until the end of anesthesia, or at least until recovery of the TOF ratio to 0.9. Stabilization and calibration of the TOF-Watch SX were performed according to good clinical research practice in pharmacodynamic studies of NMBD.¹⁵ During that time (3–10 min) patients' lungs were ventilated via face mask with oxygen/air at normocapnia. Neuromuscular data were collected via a transducer fixed to the top of the thumb using the TOF-Watch SX Monitoring Program. After set-up and stabilization of the TOF-Watch SX, a single bolus dose of IV vecuronium

*Some data from the rocuronium arm of the study have been presented. Blobner M, Eriksson L, Scholz J, Hillebrand H, Pompei L. Sugammadex (2.0 mg/kg) significantly faster reverses shallow rocuronium-induced neuromuscular blockade compared with neostigmine (50 mcg/kg). *Eur J Anaesthesiol* 2007;24(suppl 39):125.

0.1 mg/kg was administered within 10 s into a fast-running infusion, and tracheal intubation was performed after onset of complete blockade. Maintenance doses of vecuronium (0.02–0.03 mg/kg) could be administered as needed at reappearance of the second twitch (T_2) of the TOF (as indicated by the TOF-Watch SX) if clinically required.

At reappearance of T_2 after the last dose of vecuronium, either sugammadex 2 mg/kg (the recommended dose for reversal of shallow vecuronium) or neostigmine 50 $\mu\text{g}/\text{kg}^{16}$ (to a maximum of 5 mg) plus glycopyrrolate 10 $\mu\text{g}/\text{kg}$ were administered in a randomized order as an IV bolus within 10 s. The sevoflurane concentration at the time of reversal was maintained at <1.5 of MAC (0.3–2.8 vol % end-tidal) until recovery of the TOF ratio to 0.9. Sevoflurane was discontinued before tracheal extubation, which was only performed on recovery of the TOF ratio to 0.9. Immediately after tracheal extubation, patients' levels of consciousness were assessed; i.e., whether they were awake and orientated, arousable with minimal stimulation, or responsive only to tactile stimulation. For patients considered cooperative, a 5-s head-lift test and a check for general muscle weakness were performed. These evaluations were repeated every 15 min thereafter until the first head-lift test was achieved. Neuromuscular monitoring was stopped when TOF 0.9 was reached or continued until the end of surgery, depending on the length of the procedure and the preference of the anesthesiologist in charge.

Central body temperature was maintained at $\geq 35^\circ\text{C}$. Heart rate and noninvasive arterial blood pressure measurements were performed continuously and recorded at stable anesthesia, just before administration of vecuronium, at 2, 5, 10, and 30 min after administration of sugammadex or neostigmine and at the postanesthetic visit.

Postanesthetic oxygen saturation and respiratory rate were monitored as part of clinical routine for a minimum of 60 min in the recovery room. Three 10 mL blood samples were collected for safety analysis just before administration of vecuronium, at 4–6 h after administration of sugammadex or neostigmine and at the postanesthetic visit. Urine samples were collected for urinalysis on the day before surgery or just before leaving for the operating room and at the postanesthetic visit, and a physical examination was performed during the 7 days before surgery and at the postanesthetic visit.

Efficacy Variables

The primary efficacy variable was the time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.9. Secondary efficacy variables included the time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, time to recovery of the TOF ratio to 0.8, and assessments of clinical signs of recovery (level of consciousness, 5-s head-lift test, and general

muscle weakness) before transfer to the recovery room after tracheal extubation and before discharge from the recovery room.

Safety Assessments

Safety assessments included pretreatment events (from signing informed consent until administration of sugammadex or neostigmine), serious trial procedure-related events (up to 7 days postdose), and vital signs (heart rate and arterial blood pressure) at screening, prevecuronium, presugammadex, or neostigmine and at 2, 5, 10, and 30 min postdose, and at the postanesthetic visit. Blood samples were assessed for abnormalities in routine biochemistry. Urinalysis included analysis of microalbumin, β_2 -microglobulin, and *N*-acetyl glucosaminidase levels.

Adverse events and serious adverse events were recorded from the time of administration of sugammadex or neostigmine up to 7 days postdose, and any clinically significant changes on physical examination between the first assessment and the postanesthetic assessment were recorded. Clinical signs of possible residual paralysis or reoccurrence of neuromuscular block were also recorded.

Statistics

Efficacy analyses were performed using data from the intent-to-treat (ITT) population, which consisted of all randomized subjects who received sugammadex or neostigmine and had at least one efficacy measurement. Time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9 was analyzed using a two-way analysis of variance model in which treatment group and trial site were the factors of the model. Because it was expected that the variance of recovery times after administration of sugammadex and neostigmine would differ, the analysis of variance was applied to logarithm-transformed recovery times.^{17,18} Two-sided statistical testing was done at a significance level of 5%.

A separate analysis was also performed in which missing recovery times were imputed using a conservative approach toward sugammadex. It was considered conservative because relatively long recovery times were imputed for sugammadex subjects with missing recovery times and relatively short recovery times were imputed for neostigmine subjects (Appendix).

Because the recovery times in both groups followed a skewed distribution, and because large observations have a major influence on the arithmetic mean, this summary measure is prone to sampling error.¹⁹ However, the geometric mean is robust against large observations arising from data with skewed distribution and was warranted in the current study.¹⁹ Therefore, the

†When data are log-transformed and statistically analyzed in this way, the *P* values obtained in the analysis are related to comparison of the two geometric means, answering the question: is the ratio of the two geometric means different from one (alternative hypothesis) or not (null hypothesis)?

recovery times from administration of sugammadex or neostigmine to a TOF ratio of 0.7, 0.8, or 0.9 were summarized using the geometric mean (calculated by taking the logarithm of each subject's recovery time to TOF 0.7, 0.8, or 0.9, then calculating the arithmetic mean of the logarithm-transformed data, and finally transforming back into the original time scale by taking the antilogarithm). Data were also summarized using median and range values.

RESULTS

Baseline Characteristics

One hundred patients were enrolled in the study, of which 51 were randomized to the sugammadex group and 49 to the neostigmine group. Three subjects in the sugammadex group and four in the neostigmine group did not receive the study drug. Reasons for discontinuation in the sugammadex group were refusal of surgical procedure ($n = 1$) and TOF-Watch SX problems ($n = 2$). In the neostigmine group, patients were discontinued because of unavailability of site staff to perform the protocol ($n = 1$), randomization failure ($n = 1$), surgeon's withdrawal of consent for operating room time for the research team ($n = 1$), and a TOF-Watch SX problem ($n = 1$). Hence, 48 subjects in the sugammadex group and 45 in the neostigmine group were treated (representing the all-subjects-treated population). All treated patients had at least one efficacy measurement and therefore the all-subjects-treated population was equivalent to the ITT population. The treatment groups had similar baseline characteristics (Table 1).

Efficacy

In the ITT population, the time from start of administration of study drug to recovery of the TOF ratio to 0.9 was estimated to be 6.6 times faster with sugammadex compared with neostigmine (95% confidence interval [CI]: 4.7–9.3). Geometric mean times (95% CI) to recovery of the TOF ratio to 0.9 were 2.7 (2.2–3.3) min after sugammadex and 17.9 (13.1–24.3) min after neostigmine ($P < 0.0001$) (Table 2). The 95th percentile of the time to recovery of the TOF ratio to 0.9 was 6.95 min in the sugammadex group and 76.15 min in the neostigmine group.

In addition, the mean times to recovery of the TOF ratio to 0.7 and 0.8 were also significantly faster with sugammadex compared with neostigmine (Table 2). The 95th percentile of the time to recovery of the TOF ratio to 0.8 was 3.7 min in the sugammadex group and 41.4 min in the neostigmine group. A comparison of results for this dataset (termed the completed cases dataset), which includes only those patients providing times to TOF ratios of 0.9, 0.8, or 0.7, was made with results for an imputed data analysis dataset (times to TOF 0.9, 0.8, or 0.7 were imputed for those patients with missing values) and shows virtually no difference between the two approaches (Table 3).

Table 1. Baseline Characteristics (All-Subjects-Treated Population)

| | Sugammadex ($n = 48$) | Neostigmine ($n = 45$) |
|------------------------|----------------------------|-----------------------------|
| Age (yr), mean (SD) | 49 (16) | 50 (15) |
| Weight (kg), mean (SD) | 81 (19) | 76 (13) |
| Height (cm), mean (SD) | 173 (11) | 170 (11) |
| Gender (M/F), n (%) | 26/22 (54/46) | 21/24 (47/53) |
| ASA Class, n (%) | | |
| I | 18 (38) | 17 (38) |
| II | 27 (56) | 25 (56) |
| III | 3 (6) | 3 (7) |

Figure 1 shows the neuromuscular recovery profile for two patients after administration of sugammadex and neostigmine. Figure 2 shows the percentage of patients who had achieved a TOF ratio of 0.9 over the course of the study. In the sugammadex group, monitoring was stopped in a median (range) of 17 (1–105) min after TOF >0.9 was attained, and 13 patients (28%) were monitored for >30 min. In the neostigmine group, the TOF recordings were stopped in a median (range) of 5 (1–177) min (five subjects [11%] for >30 min) after the last TOF evaluation. Eight patients in the neostigmine group failed to achieve a TOF ratio of 0.9 during the monitoring period. Three other neostigmine patients and two sugammadex patients are not included in Figure 2 because the time to a TOF ratio of 0.9 was not available (neuromuscular monitoring was stopped prematurely 30 min after administration of study drug in one patient in the neostigmine group) or considered unreliable ($n = 2$ in both groups). Two patients receiving sugammadex had unexpectedly long recovery times to a TOF ratio of 0.9 (20 and 64 min) but were within the normal range for time to recovery to a TOF ratio of 0.8 (4.3 and 3.7 min, respectively). Before and after reversal, the sevoflurane concentrations were similar between the two groups.

Of those subjects randomized to receive sugammadex for reversal of vecuronium-induced neuromuscular blockade, and who provided evaluable data for the time to recovery to TOF 0.9 ($n = 46$), 27 received only an intubating dose and 19 received an intubating dose plus one or more maintenance doses (range, 1–15 maintenance doses). Of the evaluable patients in the neostigmine group ($n = 34$), 27 patients received only an intubating dose of vecuronium and 7 received one or more maintenance doses (range, 1–4 maintenance doses). Geometric mean time to recovery of the TOF ratio to 0.9 after administration of sugammadex was slightly shorter in patients who received an intubating dose of vecuronium only, compared with those who received at least one maintenance dose of vecuronium, whereas recovery of the TOF ratio to 0.9 after neostigmine was considerably shorter in those who received an intubating dose only (Table 4). As no comparison of the recovery times after maintenance doses was planned in the protocol, only descriptive information can be given in the above-mentioned table.

Table 2. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of-Four (TOF) Ratio to 0.9, 0.8, and 0.7 (Intent-to-Treat Population)

| | Sugammadex | Neostigmine | P |
|------------------------------|-----------------|-----------------|----------|
| Recovery of TOF ratio to 0.9 | | | |
| N | 46 ^a | 34 ^b | < 0.0001 |
| Geometric mean | 2.7 | 17.9 | |
| Median (range) | 2.1 (1.2–64.2) | 21.9 (2.9–76.2) | |
| Recovery of TOF ratio to 0.8 | | | |
| N | 46 ^a | 42 ^c | < 0.0001 |
| Geometric mean | 1.9 | 10.8 | |
| Median (range) | 1.7 (1.0–4.3) | 13.6 (2.2–59.1) | |
| Recovery of TOF ratio to 0.7 | | | |
| N | 46 ^a | 43 ^d | < 0.0001 |
| Geometric mean | 1.6 | 6.4 | |
| Median (range) | 1.4 (0.7–3.4) | 5.2 (1.9–54.3) | |

^a Data excluded from two patients as TOF data to 0.9, 0.8, and 0.7 were considered unreliable because of unstable TOF baseline.

^b Data excluded from 11 patients because TOF data to 0.9 were missing (8 patients failed to achieve a TOF ratio of 0.9, 1 patient did not have a recovery time measured for TOF to 0.9, and in 2 patients the TOF data to 0.9 were considered unreliable because of unstable TOF baseline).

^c Data excluded from three patients as TOF data to 0.8 were either missing (two patients) or considered unreliable because of unstable TOF baseline (one patient).

^d Data excluded from two patients as TOF data to 0.7 were either missing (one patient) or considered unreliable because of unstable TOF baseline (one patient).

Table 3. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of-Four (TOF) Ratio to 0.9, 0.8, and 0.7 in Completed Cases and Imputed Data (Intent-to-Treat Population)

| Recovery of TOF ratio to | Analysis using | Sugammadex Geometric mean | Neostigmine Geometric mean | Estimated treatment effect ^a (95% CI) |
|--------------------------|-----------------|---------------------------|----------------------------|--|
| 0.9 | Completed cases | 2.7 (n = 46) | 17.9 (n = 34) | 6.6 (4.7, 9.3) |
| | Imputed data | 2.8 (n = 48) | 16.8 (n = 45) | 6.7 (5.0, 9.1) |
| 0.8 | Completed cases | 1.9 (n = 46) | 10.8 (n = 42) | 5.9 (4.4, 8.0) |
| | Imputed data | 2.0 (n = 48) | 10.2 (n = 45) | 5.4 (4.0, 7.2) |
| 0.7 | Completed cases | 1.6 (n = 46) | 6.4 (n = 43) | 4.2 (3.1, 5.6) |
| | Imputed data | 1.6 (n = 48) | 6.1 (n = 45) | 3.9 (2.9, 5.2) |

CI = confidence interval.

^a Treatment effect is defined here as the ratio of the geometric mean recovery time after neostigmine over the geometric mean recovery time after sugammadex. Estimate for treatment effect is obtained from analysis of variance on log-transformed data.

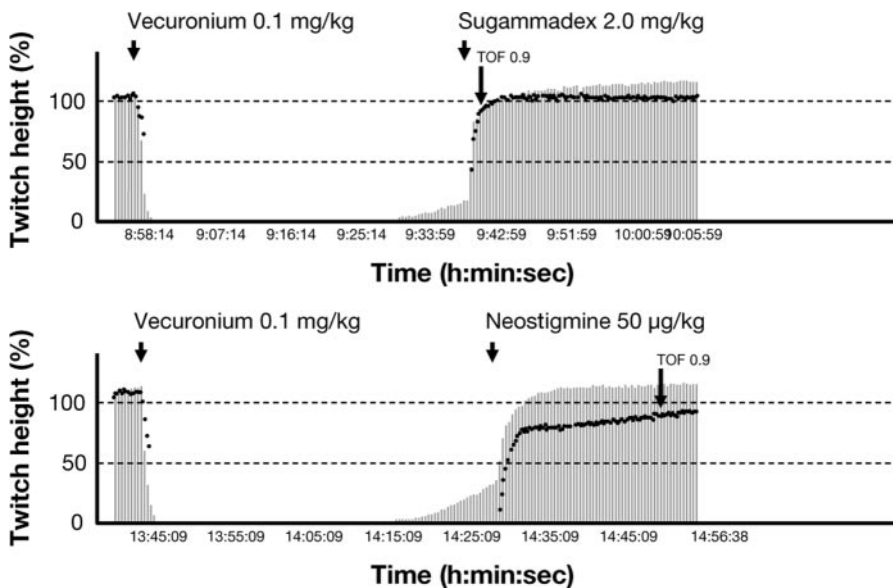


Figure 1. Examples of recovery profiles for vecuronium 0.1 mg/kg after administration of sugammadex 2.0 mg/kg or neostigmine 50 µg/kg at reappearance of second twitch (T_2). Bars represent first twitch (T_1) values (twitch height %) and dots the train-of-four (TOF [T_4/T_1]) ratio. TOF 0.9 arrow represents the time to attain a TOF ratio of 0.9 after administration of sugammadex and neostigmine, $P < 0.0001$ (for the difference between the geometric means for the two groups).

In terms of clinical signs of recovery, 29 of 48 patients (60.4%) in the sugammadex group and 26 of 45 patients (57.8%) in the neostigmine group were awake and oriented before transfer to the recovery room, and all except 7 patients in each group were cooperative. Only one patient in the sugammadex

group and six in the neostigmine group were unable to perform the 5-s head lift before transfer to the recovery room, and general muscle weakness was reported in four and six patients in each group, respectively. Before discharge from the recovery room, the clinical signs of recovery were similar in

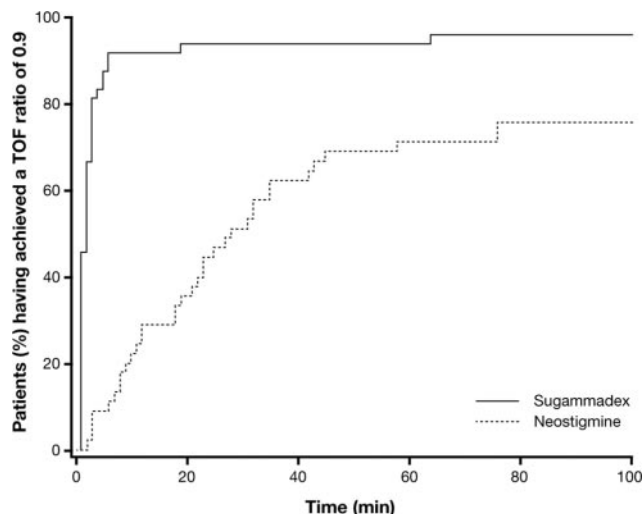


Figure 2. Percentage of patients having achieved a train-of-four (TOF) ratio to 0.9 after reversal of vecuronium-induced neuromuscular blockade with sugammadex or neostigmine (intent-to-treat population). Patients with missing data are not included. Time to TOF ratio of 0.9 = the time from start of administration of sugammadex or neostigmine to TOF ratio of 0.9.

both groups. Except for one subject in the neostigmine group, who was arousable with minimal stimulation, all patients were awake and oriented, cooperative, and able to perform the 5-s head lift, and none had general muscle weakness.

Safety

There were no serious adverse events or serious trial procedure-related events in this study. No patients discontinued from the trial because of an adverse event. Seventeen patients experienced one or more adverse events that were considered by the investigator to be possibly, probably, or definitely related to study drug: 7 (14.6%) in the sugammadex group and 10 (22.2%) in the neostigmine group.

Drug-related adverse events occurring in each group are summarized in Table 5. All of these were mild or moderate in nature except for two events in the neostigmine group that were classified by the investigator as severe: one case of prolonged neuromuscular blockade and one sleeping disorder. None of

the drug-related events was reported as a serious adverse event.

Overall, there were no marked differences in routine laboratory variables between the sugammadex and neostigmine groups.

Mean values for systolic and diastolic blood pressure and heart rate from the screening visit to the postanesthetic visit were similar in both treatment groups. Higher mean diastolic blood pressure at 2 min postdose with neostigmine (64 vs 59 mm Hg) and a faster heart rate with neostigmine at 2 min (74 vs 61 bpm) and 5 min postdose (70 vs 62 bpm) compared with sugammadex were observed (Figs. 3 and 4). Central body temperature was maintained at $\geq 35^{\circ}\text{C}$ in all patients except one in the neostigmine group and two in the sugammadex group. As the temperature deviations were only minor and for short periods, these were not considered to have an effect on recovery in these patients.

There was no clinical evidence of reoccurrence of neuromuscular block or residual neuromuscular blockade in either group.

DISCUSSION

The results of this randomized, actively controlled study demonstrate that sugammadex achieves reversal of vecuronium-induced neuromuscular blockade significantly more rapidly than neostigmine. The (geometric) mean times to achieve a TOF ratio of 0.9 with sugammadex and neostigmine were 2.7 and 17.9 min, respectively, resulting in a reversal time that was almost seven times faster with sugammadex compared with neostigmine.

The results presented are for completed cases only; that is, patients for whom recovery times to the respective TOF ratio of 0.7, 0.8, or 0.9 were available. Another analysis was also done in which missing recovery times were imputed using a conservative approach for sugammadex and a best-case scenario for neostigmine. There was no statistical difference between the completed cases analysis reported here and the imputed data analysis.

The geometric mean time to reversal of neuromuscular blockade (TOF of 0.9) with sugammadex 2.0

Table 4. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of Four (TOF) Ratio to 0.9 for Patients Who Received an Intubating Dose Only and Those Who Received at Least One Maintenance Dose of Vecuronium (Exploratory Analysis of the Intent-to-Treat Population)

| | Sugammadex group | | Neostigmine group | |
|------------------------------|----------------------|--------------------------------------|----------------------|--------------------------------------|
| | Intubating dose only | Intubating dose and maintenance dose | Intubating dose only | Intubating dose and maintenance dose |
| Recovery of TOF ratio to 0.9 | | | | |
| N | 27 ^a | 19 ^a | 27 ^b | 7 ^b |
| Geometric mean | 2.3 | 3.5 | 15.9 | 28.0 |
| Median (range) | 1.9 (1.2–64.2) | 3.4 (1.7–19.8) | 18.9 (2.9–76.2) | 35.7 (6.2–76.2) |

^a Data excluded from one patient in each group of the sugammadex cohort ($n = 48$) because TOF data to 0.9 were considered unreliable.

^b Data excluded from five patients in the intubating dose only group and six patients in the intubating plus maintenance doses group of the neostigmine cohort ($n = 45$) either because the time to recovery data were unavailable or because the TOF data to 0.9 were considered unreliable.

Table 5. Incidence (Number [%] of Patients) of Drug-Related^a Adverse Events (All-Subjects-Treated Population)

| | Sugammadex (n = 48) | Neostigmine (n = 45) |
|--|------------------------|-------------------------|
| Chills | 2 (4.2) | 0 (0) |
| Nausea | 2 (4.2) | 2 (4.4) |
| Procedural hypertension | 2 (4.2) | 1 (2.2) |
| Vomiting | 2 (4.2) | 0 (0) |
| Vertigo | 1 (2.1) | 0 (0) |
| Headache | 1 (2.1) | 0 (0) |
| Retching | 1 (2.1) | 0 (0) |
| Airway complication of anesthesia | 1 (2.1) | 0 (0) |
| Postprocedural nausea | 1 (2.1) | 0 (0) |
| Hot flush | 1 (2.1) | 0 (0) |
| Body temperature increased | 1 (2.1) | 0 (0) |
| Procedural complication (i.e., increased/decreased heart rate) | 0 (0) | 4 (8.9) |
| Dry mouth | 0 (0) | 4 (8.9) |
| Neuromuscular blockade prolonged | 0 (0) | 2 (4.4) |
| Supraventricular extrasystoles | 0 (0) | 1 (2.2) |
| Ventricular extrasystoles | 0 (0) | 1 (2.2) |
| Sleep disorder | 0 (0) | 1 (2.2) |
| Erythema | 0 (0) | 1 (2.2) |
| γ-Glutamyltransferase increased | 0 (0) | 1 (2.2) |
| Heart rate increased | 0 (0) | 1 (2.2) |

^a Considered by the investigator to be possibly, probably, or definitely related to study drug.

mg/kg in this study was in line with the results observed previously in a dose-finding study, in which sugammadex 2.0 mg/kg administered at reappearance of T_2 was found to reverse neuromuscular blockade at a mean time of 2.3 min, after administration of the same dose of vecuronium (0.1 mg/kg) under anesthesia with a target-controlled infusion of propofol.¹¹ These results suggest that after vecuronium-induced neuromuscular blockade time to recovery from sugammadex administration to a TOF ratio of 0.9 is in the range of 2–3 min. In comparison, even faster recovery times, in the range of 1–2 min, have been observed for reversal of rocuronium-induced blockade with sugammadex.^{9–12}

Recovery to a TOF ratio of at least 0.9 is now considered to be the “gold standard” for neuromuscular recovery after administration of NMBD.^{15,19,20} For this reason, time to achieve a TOF ratio of 0.9 was selected as the primary efficacy end-point in this study. Although the use of acceleromyography is more prone to artifacts than mechanomyography, it is widely accepted for research.¹⁵ As it is easier to use in the clinical setting, neuromuscular monitoring was performed with acceleromyography in this study, in accordance with previous sugammadex trials.

Neostigmine should only be administered when some signs of recovery from neuromuscular block occur^{15,16} and therefore reappearance of T_2 (measured by the TOF-Watch SX) was chosen. This approach might

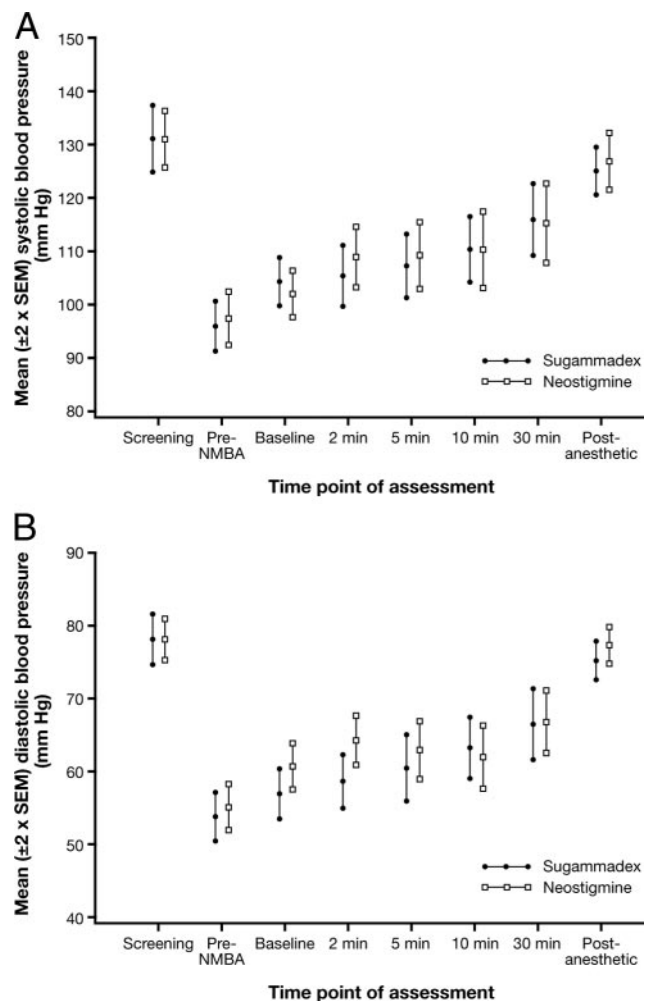


Figure 3. Mean systolic (A) and diastolic (B) blood pressure rate before (at screening, preneuromuscular blocking agent [NMBA], and baseline) and after administration (at timepoints shown) of sugammadex or neostigmine (all-subjects-treated population). SEM = standard error of the mean.

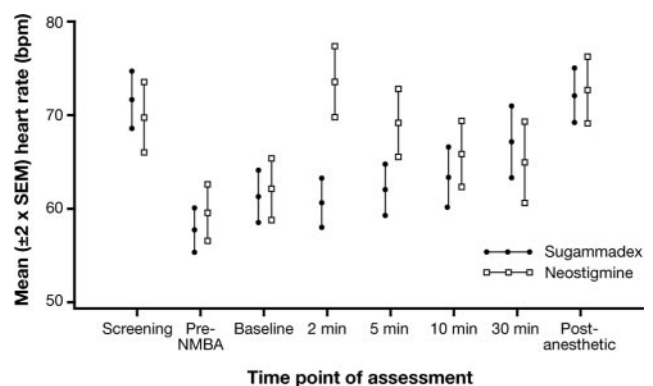


Figure 4. Mean heart rate before (at screening, preneuromuscular blocking agent [NMBA], and baseline) and after administration (at timepoints shown) of sugammadex or neostigmine (all-subjects-treated population). SEM = standard error of the mean.

enable transfer of the data obtained in this study into clinical practice. Many clinicians unfortunately still only use a peripheral nerve stimulator for monitoring of neuromuscular function and reappearance of the T_2 can

also be determined with nonquantitative monitoring devices.

Residual neuromuscular blockade may be observed in patients in the recovery room after surgery and has been shown to be associated with significant morbidity.^{1,3,21,22} In one study, residual blockade defined as a TOF ratio <0.9 was reported on arrival in the recovery room in 45% of patients administered a single intubating dose of an intermediate acting NMBD without reversal, and 16% of patients had a TOF ratio as low as <0.7 .²² There was no clinical evidence of residual neuromuscular blockade in our study after reversal with either sugammadex or neostigmine. Eight patients in the neostigmine group failed to achieve a TOF of ≥ 0.9 ; sevoflurane was discontinued in these patients either because recovery took too long or surgery was finished and tracheal extubation was performed before a TOF ratio of 0.9 (and occasionally 0.8) was reached. This prolonged recovery and early tracheal extubation may be associated with a possible risk of residual paralysis. However, even after early reversal of high-dose rocuronium (1.2 mg/kg) with sugammadex, adequate TOF values were sustained,²³ with no evidence of reparable paralysis. Failure to achieve a TOF of ≥ 0.9 in some neostigmine patients in the current study may have been related to the use of sevoflurane, which has been shown to enhance the effect of NMBDs²⁴ and to delay reversal of neuromuscular blockade with neostigmine.²⁵ In contrast, all patients in the sugammadex group achieved a TOF of ≥ 0.9 , although two patients did have unexpectedly long recovery times (20 and 64 min). A possible effect of hypothermia could be excluded because central core temperature and skin temperature above the thenar muscle remained above 35°C and 33°C, respectively. Whether this was a prolonged recovery from neuromuscular blockade or the effect of sevoflurane is unknown. Both patients recovered clinically. Previous results suggest that sevoflurane does not have an effect on the action of sugammadex when administered for reversal at T_2 .¹² For one of the patients with outlying recovery times, time to achieve a TOF of ≥ 0.9 on three consecutive TOF stimulations was prolonged, although the TOF ratio returned to 0.7 and 0.8 after 2.2 and 3.7 min, respectively. TOF recovery was defined by the first of three consecutive TOF values. The first TOF ≥ 0.9 was reached at 8.7 min; the curve then varied between TOF 0.79 and 0.93 with three consecutive TOF values of ≥ 0.9 being reached after only 64 min. For the other patient, the TOF ratio returned to 0.7 and 0.8 after 2.3 and 4.3 min, respectively, but a plateau TOF ratio of 0.85–0.87 was observed for 10 min. Thus, the 95th percentile of the time to recovery of the TOF ratio to 0.8 was only 3.7 min in the sugammadex group, much shorter than the 95th percentile of the time to recovery of the TOF ratio to 0.9 of 6.95 min. In contrast, the 95th percentile of the time to recovery of the TOF ratio to 0.8 was 41.4 min in the neostigmine group. Although

the use of sevoflurane may have influenced the recovery time as it enhances the effect of NMBDs, it was selected because it is an inhaled drug frequently used in clinical practice. Sevoflurane concentrations administered during recovery were in the same range (and always below 1.5 MAC) in both groups.

Table 4 shows that the geometric mean recovery time to TOF ratio of 0.9 for patients who received an intubating dose of vecuronium is only slightly shorter compared with patients who also received one or more maintenance doses. Because of the small number of patients who received maintenance doses, no statistical analysis was planned or performed. There was no apparent correlation between recovery time and number of maintenance doses administered. The only patient who received 15 maintenance doses of vecuronium followed by sugammadex recovered in 1.7 min, one of the fastest recovery times in the sugammadex group. Also, in the case of neostigmine, the recovery time to TOF ratio of 0.9 did not increase with an increasing number of maintenance doses.

The incidence and profile of drug-related adverse events was generally low and similar in the sugammadex and neostigmine groups, and there were no reports of serious adverse events. Overall, the incidence of drug-related adverse events was slightly higher in the neostigmine group compared with the sugammadex group (22.2% vs 14.6% of patients), and this was largely accounted for by a higher incidence of dry mouth (four cases) and procedural complications of mild-to-moderate intensity (one case of bradycardia and three cases of increased heart rate). The similar tolerability profile of sugammadex and neostigmine reported in this study was unexpected given the fact that, in contrast to neostigmine, sugammadex does not affect cholinergic transmission and is therefore unlikely to cause cholinergic side effects.²⁶ However, it should be noted that this study was not specifically designed to evaluate any differences between sugammadex and neostigmine in terms of cardiovascular or other side effects and therefore no comparative statistics were applied here.

Evaluation of changes in vital signs during the study do suggest, however, that sugammadex may be associated with fewer hemodynamic effects compared with neostigmine. Although the course for mean systolic blood pressure was similar in both groups, the increase in mean diastolic blood pressure at 2 min postdose was higher with neostigmine compared with sugammadex, as was the increase in mean heart rate at 2 and 5 min postdose.

In conclusion, the results of this study show that under sevoflurane anesthesia sugammadex is significantly more effective than neostigmine for recovery from neuromuscular blockade induced by vecuronium.

APPENDIX

Method for Imputation of Missing Recovery Times

In cases where times from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9 were missing, values were imputed using a conservative approach for sugammadex. Thus, relatively long recovery times were imputed for sugammadex subjects and relatively short recovery times were imputed for neostigmine subjects with missing recovery times.

Cases Where Times to TOF Ratio of 0.9 were Missing

If the time to recovery of the TOF ratio of 0.8 was available, then imputation of the time to a TOF ratio of 0.9 was performed as follows:

- Sugammadex group: for all subjects who were randomized to receive sugammadex and had times to recovery of the TOF ratio to 0.8 and 0.9, the difference between these two recovery times was determined. The 95th percentile (representing a long time interval for recovery from TOF 0.8 to 0.9) of these differences was calculated and then added to the time to recovery of the TOF ratio to 0.8.
- Neostigmine group: the same procedure as for sugammadex subjects with missing times was performed but only subjects randomized to receive neostigmine were used, the 5th percentile (representing a short time interval for recovery from TOF 0.8 to 0.9) of the differences in time to recovery of the TOF ratio to 0.8 and 0.9 was calculated, and added to the time to recovery of the TOF ratio to 0.8.
- If, for a given subject, the times from the start of administration of study drug to recovery of the TOF ratio to 0.8 were also missing but the time to the TOF ratio of 0.7 was available, then imputation of the time to a TOF ratio of 0.9 was performed as follows:
- Sugammadex group: for all subjects who were randomized to sugammadex and had times to recovery of the TOF ratio to 0.7 and 0.9 available, the difference between these two recovery times was determined. The 95th percentile of these differences was calculated and then added to the time to recovery of the TOF ratio to 0.7.
- Neostigmine group: the same procedure as for sugammadex subjects was performed, but only subjects randomized to receive neostigmine were used, the 5th percentile of the differences in time to recovery of the TOF ratio to 0.7 and 0.9 was calculated, and added to the time to recovery of the TOF ratio to 0.7.
- For all sugammadex-treated patients where the times to recovery of the TOF ratio to 0.9, 0.8, and 0.7 were unavailable, the imputed time for recovery to a TOF ratio of 0.9 was the 95th percentile of

the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive sugammadex. Similarly, for all neostigmine-treated patients where the time to recovery of the TOF ratio to 0.9, 0.8, and 0.7 was unavailable, the imputed time for recovery to a TOF ratio of 0.9 was the 5th percentile of the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive neostigmine.

Cases Where Times to TOF Ratio of 0.8 were Missing

Imputation of missing times from the start of administration of study drug to recovery of the TOF ratio to 0.8 followed a corresponding procedure to that used for missing times to a TOF ratio of 0.9: the 95th percentile (sugammadex) or 5th percentile (neostigmine) of the differences in time between recovery of the TOF ratio to 0.7 and 0.8 was used.

Cases Where Times to TOF Ratio of 0.7 were Missing

The 95th percentile observed time for subjects randomized to sugammadex and 5th percentile observed time for subjects randomized to neostigmine were imputed for subjects in whom the time to recovery of the TOF ratio to 0.7 was unavailable.

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A Randomized, Dose-Response Study of Sugammadex Given for the Reversal of Deep Rocuronium- or Vecuronium-Induced Neuromuscular Blockade Under Sevoflurane Anesthesia

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BACKGROUND: Sugammadex is the first of a new class of selective muscle relaxant binding drugs developed for the rapid and complete reversal of neuromuscular blockade induced by rocuronium and vecuronium. Many studies have demonstrated a dose-response relationship with sugammadex for reversal of neuromuscular blockade in patients induced and maintained under propofol anesthesia. However, sevoflurane anesthesia, unlike propofol, can prolong the effect of neuromuscular blocking drugs (NMBDs) such as rocuronium and vecuronium.

METHODS: We designed this randomized, open-label, dose-response trial to explore the dose-response relationship of sugammadex for the reversal of deep neuromuscular blockade induced by rocuronium or vecuronium under propofol-induced and sevoflurane-maintained anesthesia. As a secondary objective, the safety variables of sugammadex were evaluated. After anesthesia induction with propofol, 102 patients aged ≥ 20 and < 65 yr were randomized to receive a single bolus dose of rocuronium 0.9 mg/kg ($n = 50$) or vecuronium 0.1 mg/kg ($n = 52$), followed by maintenance doses (rocuronium 0.1–0.2 mg/kg or vecuronium 0.02–0.03 mg/kg) as needed. Neuromuscular blockade was monitored using acceleromyography. After the last dose of NMBD, at 1–2 posttetanic counts, a single bolus dose of sugammadex 0.5, 1.0, 2.0, 4.0, or 8.0 mg/kg was administered. The primary efficacy variable was time from start of sugammadex administration to recovery of the T_4/T_1 ratio to 0.9.

RESULTS: The per-protocol population consisted of 48 patients in the rocuronium group and 47 in the vecuronium group. A dose-response effect was demonstrated for decreased mean time to recovery of the T_4/T_1 ratio to 0.9 with increasing sugammadex dose in both NMBD groups (per-protocol population): rocuronium group, 79.8 (sd 33.0) min (sugammadex 0.5 mg/kg) to 1.7 (0.7) min (4.0 mg/kg) and 1.1 (0.3) min (8.0 mg/kg subgroup); vecuronium group, 68.4 (31.9) min (0.5 mg/kg) to 3.3 (3.5) min (4.0 mg/kg), and 1.7 (0.8) min (8.0 mg/kg subgroup). Neuromuscular monitoring showed recurrent neuromuscular blockade in 5 patients, all in the rocuronium group (2 given sugammadex 0.5 mg/kg and 3 given 1.0 mg/kg), but there were no clinical events attributable to recurrent or residual neuromuscular blockade.

CONCLUSION: Sugammadex at doses of ≥ 4 mg/kg provides rapid reversal of deep rocuronium- and vecuronium-induced neuromuscular blockade under sevoflurane maintenance anesthesia.

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Sugammadex is a modified, specifically designed γ -cyclodextrin, the first of a new class of selective relaxant binding drugs developed for the rapid and complete reversal of neuromuscular blockade induced by the

aminosteroid neuromuscular blocking drugs (NMBDs), rocuronium and vecuronium.^{1–3} By forming complexes with NMBDs, sugammadex prevents them from binding to nicotinic receptors in the neuromuscular junctions and hence reverses their effects.^{1,4}

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Clinical studies of sugammadex in surgical patients conducted and published thus far have shown that sugammadex provides effective, dose-dependent reversal of both moderate and deep/intense rocuronium-induced neuromuscular blockade, but most studies have been conducted under propofol maintenance anesthesia.⁵⁻⁹ Two studies have been published in which surgical patients received sugammadex under sevoflurane maintenance anesthesia, with similar efficacy and safety assessments to the current study.^{10,11} These studies were not dose-finding studies and investigated only 1 dose of sugammadex. A dose-response relationship of sugammadex for reversal of vecuronium-induced neuromuscular moderate blockade has been described but only under propofol maintenance anesthesia.³ Thus, although sevoflurane is widely used in clinical practice and enhances neuromuscular blockade, the safety and efficacy of various doses of sugammadex under maintenance anesthesia with volatile drugs remain largely unknown, especially after administration at deep neuromuscular blockade. This study was designed to explore the full dose-response relationship of sugammadex when administered at deep rocuronium- or vecuronium-induced neuromuscular blockade in surgical patients under maintenance anesthesia with sevoflurane. In addition, safety variables (particularly adverse event [AE] information) of sugammadex were assessed.

METHODS

Study Design and Patient Selection

This Phase II, multicenter, randomized, open-label, parallel, dose-response trial was conducted between October 2005 and May 2006. The protocol was approved by the Independent Ethics Committee of each center, and the trial was conducted according to the ethical principles in the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and current regulatory requirements.

Patients were eligible for entry into the trial if they were at least 20 yr but <65 yr of age, ASA physical status I-III, and were scheduled for elective surgery requiring muscle relaxation, in a supine position under sevoflurane anesthesia, with an anticipated duration of about 1.5-3.0 h. Only patients who had given written informed consent were included.

Patients were excluded from entry into the study if they were expected to have a difficult tracheal intubation because of anatomical malformations; had known or suspected neuromuscular disorders impairing neuromuscular blockade, and/or significant renal dysfunction (e.g., creatinine level >1.6 mg/dL), and/or severe hepatic dysfunction; had a known or suspected (family) history of malignant hyperthermia, or an allergy to narcotics, muscle relaxants, or other medication used during general anesthesia. Patients receiving medication expected to interfere with the NMBDs used in this trial were also excluded, as were those

who had already participated in a previous sugammadex trial or other trial not approved by the sponsor, within 6 mo of this trial. Female patients who were pregnant, breast-feeding, or of childbearing age using hormonal contraception or no means of birth control were also excluded.

Patients complying with all inclusion and exclusion criteria were randomly assigned to rocuronium or vecuronium and then to 1 of the sugammadex dose groups. The randomization was performed with a secure web site providing randomization number, allocation to reversal from rocuronium or vecuronium, and the treatment dose of sugammadex.

Study Procedures

An IV cannula was inserted into the vein of each forearm, 1 for administration of anesthetic drugs, rocuronium, vecuronium, and sugammadex, and the second for blood sampling at predefined time points for biochemistry/hematology analyses. Anesthesia was induced with IV propofol and an opioid and maintained using sevoflurane and an opioid, both according to each patient's need. Nitrous oxide could be administered. Other anesthetic practices were consistent with routine procedures at each site, and drugs and doses were adjusted to provide optimal patient care.

After induction of anesthesia and before administration of vecuronium or rocuronium, monitoring of neuromuscular transmission at the adductor pollicis muscle was initiated using acceleromyography (TOF-Watch® SX, Schering-Plough Ireland, Dublin, Ireland). After degreasing the skin, 2 pediatric surface electrodes (Neotrode®, ConMed, Utica, NY) were placed above the ulnar nerve near the wrist. A 50-Hz tetanic stimulation was applied for 5 s and followed after 1 min by train-of-four (TOF) stimulation every 15 s. When the response to TOF was stable, calibration and supramaximal stimulation was ensured by the built-in calibration function (CAL 2). Stable baseline of the response to TOF was documented for at least 2 min before the NMBD was administered. Neuromuscular data were collected via a transducer fixed to the top of the thumb and transferred online to a computer using the TOF-Watch® SX Monitoring Program. Neuromuscular monitoring was continued until the end of anesthesia and at least until recovery of the TOF T_4/T_1 ratio to 0.9.

After calibration and stabilization of the TOF-Watch® SX, a single bolus dose of rocuronium 0.9 mg/kg or vecuronium 0.1 mg/kg was administered, according to the randomization schedule, within 10 s into a fast-running IV infusion. These doses were selected because they are the recommended doses for tracheal intubation. After administration of the NMBD, tracheal intubation was performed. Maintenance doses of rocuronium (0.1-0.2 mg/kg) or vecuronium (0.02-0.03 mg/kg) were given as needed to maintain a target depth of neuromuscular blockade at 1-2 posttetanic counts (PTCs). After administration of

the last dose of NMBD, with neuromuscular blockade at a target of 1–2 PTCs, a single bolus dose of sugammadex 0.5, 1.0, 2.0, 4.0, or 8.0 mg/kg was administered within 10 s into a fast-running IV infusion. Administration at PTC 0 or >6 was considered a major protocol violation. Patients were not permitted to receive any other reversal drug (e.g., neostigmine, edrophonium) or muscle relaxant other than rocuronium (rocuronium group) or vecuronium (vecuronium group) before recovery of the T_4/T_1 ratio to 0.9. If further muscle relaxation was needed after administration of sugammadex, a nonsteroidal muscle relaxant was administered. If the time from sugammadex administration to recovery to a T_4/T_1 ratio of 0.9 was longer than 1.5 h, neostigmine or edrophonium for reversal could be considered.

Consciousness was assessed on admission to the recovery room and at 2 h after admission, and clinical assessments of recovery (assessment of 5-s head lift, diplopia, tongue-depressor test, and general muscle weakness) were performed in fully awake and oriented patients.

Safety Assessments

Patients were monitored for AEs, serious AEs (SAEs), and serious trial procedure-related events (SPEs) from the time of administration of vecuronium or rocuronium up to the end of the trial period (the seventh postoperative day). At the second and seventh postoperative days, contact was made either by phone or visit (if still hospitalized) to inquire regarding each patient's well-being. All AEs, SAEs, and SPEs as described by the investigator were coded using MedDRA (Medical Dictionary for Regulatory Activities, version 9.0).

Safety assessments also included monitoring of medical device (near) incidents, laboratory variables, physical examinations, and vital signs. Vital signs (heart rate and arterial blood pressure) were recorded at screening, just before administration of rocuronium or vecuronium, just before and at 2, 5, 10, and 30 min after administration of sugammadex, and at the postanesthetic visit. Respiratory rate was also recorded during screening and at the postanesthetic visit (first postoperative day). Continuous cardiac monitoring was performed according to routine anesthetic practice and any cardiovascular event considered by the investigator to be clinically significant was recorded as an AE. Central body temperature was measured continuously and was to be maintained at $\geq 35^\circ\text{C}$.

Patients were monitored for possible signs of recurrent neuromuscular blockade (decrease in T_4/T_1 from ≥ 0.9 to < 0.8 in at least 3 consecutive TOF values). Postanesthetic oxygen saturation (using a pulse oximeter) and respiratory rate were also measured, and patients were monitored for any clinical evidence of recurrent neuromuscular blockade, such as respiratory problems, for a minimum of 120 min after recovery to a T_4/T_1 ratio of 0.9. In addition, the investigator was asked

whether clinical signs of any possible interaction of sugammadex with endogenous or exogenous compounds (other than rocuronium/vecuronium) occurred, such as an unusual or unexpected drug effect, or a greater or lesser than expected response to a given dose of drug.

For the purposes of biochemistry and hematology analysis, 3 10-mL blood samples were collected from each patient just before administration of rocuronium or vecuronium, at 60 min after administration of sugammadex (or at the end of surgery), and at the postanesthetic visit. Assessments included hematocrit, blood count, hemoglobin, electrolytes, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatine kinase, alkaline phosphatase, γ -glutamyltransferase, fasting glucose, and total cholesterol.

Urine samples were collected during screening, before leaving for the operating room, and at the postanesthetic visit. Analyses included urine chemistry (i.e., pH, protein, glucose, blood, ketones, bile pigments, urobilinogen, microalbumin, β_2 -microglobulin, and *N*-acetylglucosaminidase levels) and urine sediment (i.e., cast, erythrocytes, leukocytes, epithelial cells, and crystals).

Physical examinations were performed during screening and at the postanesthetic visit, and any clinically significant changes between visits were recorded.

Statistics

The all-subjects-treated (AST) population consisted of all randomized patients who received a dose of sugammadex, and the intent-to-treat (ITT) population comprised all randomized patients who received a dose of sugammadex and had at least 1 postbaseline efficacy measurement. The per-protocol (PP) population consisted of all patients from the ITT population who had no major protocol violations, or multiple minor protocol violations leading to the exclusion of all efficacy data.

The primary efficacy variable was the time from the start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9. Secondary efficacy variables were the times from the start of administration of sugammadex to recovery of the T_4/T_1 ratios to 0.7 and to 0.8. The efficacy analyses were performed using data from the PP population, and safety analyses were performed using data from the AST population.

To achieve a success rate of 90% (based on a simulation process) and assuming that approximately 10% of patients would have 1 or more major protocol violation or missing data, it was calculated that 10 patients would need to be enrolled in each of the 5 sugammadex dose groups in both the rocuronium and vecuronium groups. Thus, 50 patients were to be randomized to rocuronium and 50 patients to vecuronium.

RESULTS

Baseline Characteristics

The trial was conducted in 7 centers in Europe: 3 in France (Creteil, Paris, Poitiers), 2 in The Netherlands

Table 1. Baseline Characteristics for the Sugammadex Dose Groups (All-Subjects-Treated Group)

| | Sugammadex dose (mg/kg) | | | | | |
|---------------------------|-------------------------|-------------|-------------|-------------|-------------|---------------|
| | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 | Total |
| Rocuronium (<i>n</i>) | 9 | 10 | 10 | 11 | 10 | 50 |
| Age (yr), mean (SD) | 49 (7) | 42 (9) | 49 (6) | 51 (13) | 52 (9) | 49 (9) |
| Weight (kg), mean (SD) | 89 (22) | 83 (13) | 76 (11) | 77 (21) | 74 (14) | 80 (17) |
| Height (cm), mean (SD) | 172 (8) | 174 (8) | 170 (6) | 171 (12) | 173 (9) | 172 (9) |
| Male/female, <i>n</i> (%) | 5/4 (56/44) | 8/2 (80/20) | 5/5 (50/50) | 5/6 (45/55) | 5/5 (50/50) | 28/22 (56/44) |
| ASA class, <i>n</i> (%) | | | | | | |
| I | 6 (67) | 5 (50) | 2 (20) | 6 (55) | 5 (50) | 24 (48) |
| II | 3 (33) | 5 (50) | 7 (70) | 5 (45) | 5 (50) | 25 (50) |
| III | 0 (0) | 0 (0) | 1 (10) | 0 (0) | 0 (0) | 1 (2) |
| Vecuronium (<i>n</i>) | 9 | 10 | 11 | 10 | 11 | 51 |
| Age (yr), mean (SD) | 44 (14) | 50 (14) | 54 (6) | 40 (11) | 50 (9) | 48 (12) |
| Weight (kg), mean (SD) | 74 (10) | 69 (13) | 83 (7) | 79 (11) | 76 (8) | 76 (11) |
| Height (cm), mean (SD) | 175 (7) | 171 (12) | 173 (8) | 182 (8) | 172 (6) | 175 (9) |
| Male/female, <i>n</i> (%) | 5/4 (56/44) | 4/6 (40/60) | 7/4 (64/36) | 7/3 (70/30) | 6/5 (55/45) | 29/22 (57/43) |
| ASA class, <i>n</i> (%) | | | | | | |
| I | 7 (78) | 8 (80) | 7 (64) | 9 (90) | 6 (55) | 37 (73) |
| II | 2 (22) | 2 (20) | 4 (36) | 1 (10) | 5 (45) | 14 (27) |
| III | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

ASA = American Society of Anesthesiologists.

(Groningen, Rotterdam), and 1 center each in Belgium (Edegem) and Denmark (Copenhagen). One hundred and two patients were enrolled in the study, 50 of whom were randomized to the rocuronium group and 52 to the vecuronium group. All patients in the rocuronium group received sugammadex and completed the trial. One patient in the vecuronium group discontinued from the study before administration of sugammadex, and another patient was not available for the Day 7 follow-up and so did not complete the trial. Therefore, both the ITT and AST groups comprised 101 patients (rocuronium *n* = 50; vecuronium *n* = 51).

There were major protocol violations in 6 patients (2 in the rocuronium group and 4 in the vecuronium group), and these patients were excluded from the PP population. In the rocuronium group, 2 patients (both randomized to sugammadex 0.5 mg/kg) were excluded because an exclusion criterion was met (*n* = 1) and because PTC data were unavailable at the time of sugammadex administration (*n* = 1). The patient without PTC data at the time of sugammadex administration received the wrong dose of sugammadex (3.7 mg/kg instead of the randomized dose of 0.5 mg/kg) and was included in the 4.0 mg/kg subgroup of the AST population. Reasons for exclusion in the vecuronium group were: disallowed medication received (8.0 mg/kg, *n* = 1); deviation of sugammadex dose by >10% from the randomized dose (received 4.5 mg/kg not 4.0 mg/kg, *n* = 1); and sugammadex was not administered at the required depth of blockade (sugammadex 0.5 and 1.0 mg/kg, *n* = 2). Thus, of the 101 subjects who received sugammadex, 98 subjects received sugammadex within the predefined window of depth of blockade (1–6 PTCs). The PP population consisted of 48 patients in the rocuronium group and 47 in the vecuronium group.

Treatment groups were similar in terms of baseline characteristics, with the exception of a higher percentage of patients categorized as ASA physical status II in the rocuronium group compared with the vecuronium group (Table 1).

Anesthesia

Duration of anesthesia ranged from approximately 1 to 5 h. In patients in the rocuronium group, the overall range of sevoflurane end-tidal concentrations given before and after sugammadex administration was 0.25%–2.9% and 0.2%–3.3%, respectively. In patients in the vecuronium group, the range of end-tidal concentrations given before and after administration of sugammadex was 0.2%–3.2% and 0.2%–3.4%, respectively. Sevoflurane was maintained at least until recovery of the T_4/T_1 ratio to 0.9 in 42 of the 50 patients (84%) treated with rocuronium and in 46 of the 51 patients (90%) treated with vecuronium. In 6 patients in the rocuronium group and 3 patients in the vecuronium group, sevoflurane was stopped before a T_4/T_1 ratio of 0.9 was achieved, and in 2 patients in the rocuronium group and 2 patients in the vecuronium group, the time to a T_4/T_1 ratio was not available because of technical issues with the monitoring of neuromuscular recovery. In the rocuronium group, the median time between start of sevoflurane and administration of sugammadex was 49.0 min. The longest time between start of sevoflurane and administration of sugammadex was 221.3 min for a patient in the 4.0 mg/kg group, and 1 patient in the 2.0 mg/kg group did not start sevoflurane until 47.2 min after sugammadex administration. In the vecuronium group, the median time between start of sevoflurane and administration of sugammadex was 41.1 min (range 11.5–165.7 min). Ten patients in the rocuronium group (20%) and 13 patients in the vecuronium group

Table 2. Mean (sd) Time (Min) and Median Time (Min) from Start of Administration of Sugammadex to Recovery of the T_4/T_1 Ratio to 0.9 (Per-Protocol Population)

| | Sugammadex dose (mg/kg) | | | | |
|-------------------------|-------------------------|----------------|------------|----------------|-----------|
| | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 |
| Rocuronium group | | | | | |
| <i>n</i> | 8 | 9 ^a | 10 | 10 | 10 |
| Mean (sd) | 79.8 (33.0) | 28.0 (43.7) | 3.2 (1.5) | 1.7 (0.7) | 1.1 (0.3) |
| Median | 87.5 | 7.4 | 3.2 | 1.5 | 1.1 |
| Min-max | 24.4–131.7 | 3.6–117.1 | 1.1–6.6 | 0.8–2.9 | 0.8–2.0 |
| Vecuronium group | | | | | |
| <i>n</i> | 7 ^a | 9 | 11 | 8 ^a | 10 |
| Mean (sd) | 68.4 (31.9) | 25.1 (24.9) | 9.1 (20.6) | 3.3 (3.5) | 1.7 (0.8) |
| Median | 59.1 | 15.7 | 2.8 | 2.3 | 1.6 |
| Min-max | 29.4–124.9 | 2.7–66.9 | 1.6–71.0 | 1.0–11.7 | 0.7–2.9 |

^a For 1 patient in the rocuronium group (sugammadex 1.0 mg/kg) and 2 patients in the vecuronium group (sugammadex 0.5 and 4.0 mg/kg), the time to recovery of the T_4/T_1 ratio to 0.9 was unavailable.

(25%) distributed across all sugammadex dose groups also received nitrous oxide.

Of the 50 subjects who were randomized to the rocuronium group, 42 received 1 intubation dose of rocuronium, and 8 received additional doses of this NMBD. Excluding 1 patient who received rocuronium and sugammadex concomitantly in error and who was excluded from the PP group because of the lack of PTC data, the time between first dose of relaxant and sugammadex ranged from approximately 25 min (1 dose) to 3.5 h (multiple doses). Of the 52 subjects who were randomized to vecuronium, 43 received 1 intubation dose and 9 received multiple doses. The time between first dose of vecuronium and sugammadex ranged from approximately 15 min (1 dose) to 1 h (multiple doses). After TOF 0.9 was achieved, neuromuscular monitoring continued for up to 30 min for half of the subjects, whereas it lasted for 30 min to 2 h in the other half of the study population.

Efficacy

Sugammadex provided a dose-dependent reduction in time to recovery of the T_4/T_1 ratio to 0.9 in both NMBD groups (Table 2). In the rocuronium group, mean recovery time to a T_4/T_1 ratio of 0.9 decreased from 79.8 min in the sugammadex 0.5 mg/kg group to 3.2 min (2.0 mg/kg), 1.7 min (4.0 mg/kg), and 1.1 min (8.0 mg/kg, PP population). In the vecuronium group, mean time to recovery of the T_4/T_1 ratio to 0.9 decreased from 68.4 min in the sugammadex 0.5 mg/kg group to 9.1 min (2.0 mg/kg), 3.3 min (4.0 mg/kg), and 1.7 min (8.0 mg/kg, PP population). These findings indicate that a plateau of recovery was attained in both NMBD groups at higher sugammadex doses (Fig. 1). In addition, marked interpatient variations in the time to recovery of the T_4/T_1 ratio to 0.9 in response to sugammadex were observed in patients who received vecuronium even at doses up to 4.0 mg/kg of sugammadex (Table 2).

A dose-dependent decrease in recovery time to a T_4/T_1 ratio of 0.7 and 0.8 with increasing sugammadex dose was also observed in both NMBD groups (Table 3).

Safety Assessments

Forty of the 50 patients (80%) in the rocuronium group and 33 of 51 patients (64.7%) in the vecuronium group, who received sugammadex, experienced at least 1 AE. There were no deaths, SPEs, or medical device (near) incidents, and no SAEs were reported that were considered related to the study drug. None of the subjects discontinued the trial because of an AE.

Three patients in the rocuronium group and 1 patient in the vecuronium group experienced at least 1 SAE. In the rocuronium group, SAEs consisted of mild intensity wound hemorrhage (sugammadex 0.5 mg/kg), mild tracheal stenosis and laryngeal edema (sugammadex 2.0 mg/kg), and severe convulsions, hypoxia, and bacterial meningitis (sugammadex 4.0 mg/kg). In the vecuronium group, the single SAE was moderate-intensity postprocedural hemorrhage (sugammadex 8.0 mg/kg). All patients recovered from the SAEs, except for 1 patient with tracheal stenosis and laryngeal edema who recovered with sequelae (tracheal stoma). None of the reported SAEs were considered related to sugammadex by the investigators. The case of laryngeal edema was attributed by the investigator to the intubation procedure and surgery (partial excision of the thyroid goiter for fibrotic thyroiditis). The case of convulsions, which occurred >6 h after administration of sugammadex and 2 h after sevoflurane was stopped, was in a patient who underwent ethmoidectomy (partial removal of the mucosal lining and bony partitions between the ethmoid sinuses) for a nasal sinus cancer. The patient received thiopental and clonazepam and the convulsions resolved within 2 min.

Twenty-three subjects experienced 1 or more AEs that were considered by the investigator to be possibly, probably, or definitely related to the study drug: 14 patients (28.0%) in the rocuronium group and 9 patients (17.6%) in the vecuronium group. There was no relationship observed between the occurrence of drug-related AEs and the dose of sugammadex. The most frequently reported drug-related AEs in the rocuronium group were nausea ($n = 8$) and procedural complications ($n = 2$). In the vecuronium group, nausea ($n = 3$) and urinary retention ($n = 2$) were the most common drug-related AEs. All were mild or moderate in nature except for 1 case of urinary retention in the vecuronium group (sugammadex 8.0 mg/kg), which was classified as severe.

Overall, hematology, biochemistry, and urinalysis variables were comparable among sugammadex doses in both the rocuronium and vecuronium groups. With respect to vital signs, no relevant differences were observed among the dose groups.

Recurrent neuromuscular blockade was reported in 5 patients in the rocuronium group, all in the 0.5 or 1.0

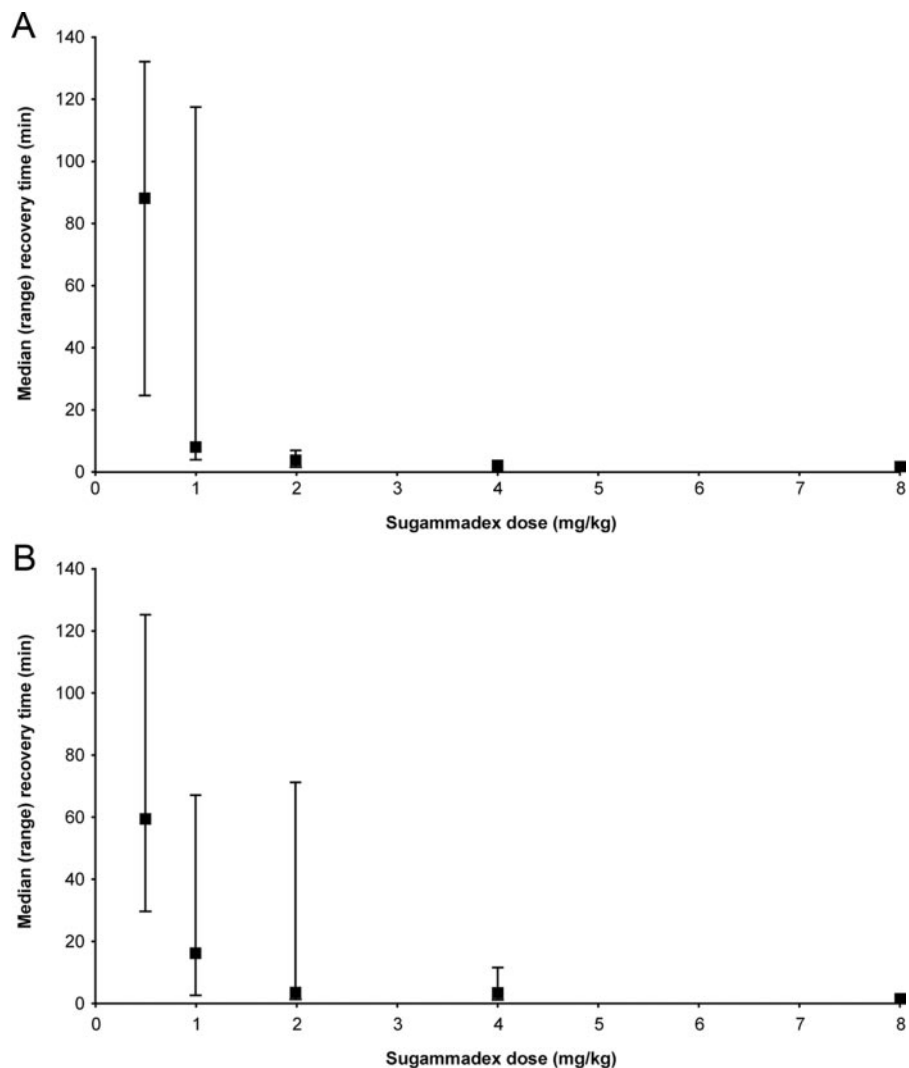


Figure 1. Time to recovery of the T_4/T_1 ratio to 0.9 after administration of sugammadex 0.5, 1.0, 2.0, 4.0, or 8.0 mg/kg at a target of 1–2 posttetanic counts after (A) rocuronium 0.9 mg/kg or (B) vecuronium 0.1 mg/kg.

mg/kg sugammadex dose groups (Table 4). A representative TOF trace for 1 of these patients is shown in Figure 2. Two patients met the predefined definition (a decrease in T_4/T_1 from ≥ 0.9 to < 0.8 in at least 3 consecutive TOF values). One of these 2 subjects who received 1.0 mg/kg sugammadex showed an initial recovery to TOF 0.9 at approximately 4 min, followed by a gradual decrease to a TOF value of 0.6 at 37 min after sugammadex. In this subject, monitoring ended before TOF 0.9 was reached. Another subject, also receiving 1.0 mg/kg sugammadex, showed initial recovery to a TOF value of 0.9 at approximately 7 min, followed by a decrease to TOF 0.6 (71 min after sugammadex) and an increase to a TOF value of 0.9 at 98 min after sugammadex administration. For 3 of the 5 subjects, the definition of recurrent blockade was not met because full recovery was not reached before the decrease. These subjects received 0.5, 0.5, and 1.0 mg/kg sugammadex, respectively, and showed an initial increase to a TOF value of 0.65, 0.8, and 0.8. After this, a gradual decrease took place, with a lowest TOF value of 0.3, 0.7, and 0.7, respectively. At 62, 88, and 91 min after sugammadex administration, a TOF

value of 0.9 was achieved. One of the cases has been published in an earlier report.¹²

No cases were reported in the vecuronium group, and no clinical events attributable to recurrent or residual neuromuscular blockade occurred in either NMBD group.

Central body temperature was maintained at $\geq 35^\circ\text{C}$ in all patients except 6 in the rocuronium group. No interaction of sugammadex with an endogenous or exogenous compound, other than rocuronium or vecuronium, was reported.

DISCUSSION

This study demonstrates that sugammadex provides dose-related reversal of deep rocuronium- or vecuronium-induced neuromuscular blockade in surgical patients under sevoflurane maintenance anesthesia. Clear dose-response effects were seen between the sugammadex dose administered after single or multiple doses of rocuronium or vecuronium, and the time to achieve a T_4/T_1 ratio of 0.9. Time to recovery of the T_4/T_1 ratio to 0.7 and 0.8 also decreased with increased sugammadex dose. Doses of sugammadex

Table 3. Mean (SD) Time (Min) and Median Time (Min) from Start of Administration of Sugammadex to Recovery of the T_4/T_1 Ratio to 0.7 and 0.8 (Per-Protocol Population)

| | Sugammadex dose (mg/kg) | | | | |
|-------------------------|-------------------------|-------------|-----------|-----------|-----------|
| | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 |
| Rocuronium group | | | | | |
| <i>n</i> | 8 | 10 | 10 | 10 | 10 |
| T_4/T_1 ratio of 0.7 | | | | | |
| Mean (SD) | 47.7 (27.6) | 4.5 (2.0) | 2.2 (1.0) | 1.3 (0.5) | 0.9 (0.3) |
| Median | 48.0 | 4.5 | 2.1 | 1.1 | 0.9 |
| Min-max | 7.0–78.7 | 2.3–8.7 | 1.0–3.9 | 0.8–2.6 | 0.5–1.5 |
| T_4/T_1 ratio of 0.8 | | | | | |
| Mean (SD) | 57.0 (33.0) | 14.2 (20.6) | 2.5 (1.1) | 1.4 (0.6) | 1.0 (0.3) |
| Median | 53.0 | 5.5 | 2.3 | 1.1 | 0.9 |
| Min-max | 9.5–102.4 | 2.6–61.4 | 1.0–4.6 | 0.8–2.6 | 0.5–1.7 |
| Vecuronium group | | | | | |
| <i>n</i> | 8 ^a | 9 | 11 | 9 | 10 |
| T_4/T_1 ratio of 0.7 | | | | | |
| Mean (SD) | 30.2 (34.7) | 4.1 (2.0) | 2.3 (1.2) | 1.7 (0.7) | 1.3 (0.6) |
| Median | 11.6 | 3.5 | 2.0 | 1.5 | 1.3 |
| Min-max | 3.1–96.4 | 2.2–8.7 | 1.1–5.2 | 0.8–2.9 | 0.6–2.2 |
| T_4/T_1 ratio of 0.8 | | | | | |
| Mean (SD) | 45.9 (29.6) | 5.1 (2.7) | 2.9 (1.8) | 2.9 (3.3) | 1.4 (0.6) |
| Median | 50.4 | 4.4 | 2.3 | 1.9 | 1.4 |
| Min-max | 4.1–90.2 | 2.2–10.2 | 1.4–7.2 | 1.0–11.4 | 0.7–2.4 |

^a *n* = 7 for time to a T_4/T_1 ratio of 0.8 in the vecuronium and sugammadex 0.5 mg/kg group, as this recovery time was unavailable in 1 patient.

of ≥ 4 mg/kg permitted reversal in ≤ 3 min in all 20 patients treated with rocuronium and in 16 of 18 (89%) treated with vecuronium. In addition, 1 patient in the vecuronium group treated with sugammadex 4.0 mg/kg had a time to reversal of just over 3 min (3 min, 2 s).

The objective of the study was to establish the dose-response relationship of sugammadex given as a reversal drug of rocuronium or vecuronium at a deep neuromuscular blockade (1–2 PTCs). A comparison between the recovery times observed for rocuronium and vecuronium was not part of the original statistical analysis plan; however, this study suggests that doses of ≥ 4 mg/kg sugammadex result in rapid reversal of both deep rocuronium- and vecuronium-induced blockade, allowing recovery to a TOF ratio of 0.9 in a

median (range) of 1.5 min (0.8–2.9 min) after rocuronium and 2.3 min (1.0–11.7 min) after vecuronium.

The findings of this study compare favorably with those from a Phase II study in surgical patients investigating the effects of sugammadex on the reversal of deep rocuronium-induced neuromuscular blockade by Groudine et al.⁸ In that study, sugammadex effectively and safely reversed deep neuromuscular blockade in 50 patients given sugammadex (0.5–8.0 mg/kg) after deep block induced by rocuronium (0.6 or 1.2 mg/kg). As in the current study, sugammadex was given at a PTC of 1–2. Mean times to recovery of the TOF ratio to 0.9 decreased with increasing sugammadex dose, with a mean recovery time of 1.2 min observed at the highest sugammadex dose.

Our study differs from the study by Groudine et al.⁸ in that sevoflurane was used as the maintenance anesthetic rather than propofol. Sevoflurane enhances the neuromuscular blocking effect of rocuronium.^{13–15} Therefore, theoretically, the efficacy of sugammadex in reversing rocuronium-induced neuromuscular blockade may be diminished under sevoflurane anesthesia. However, sugammadex seems equally effective for reversal of rocuronium-induced neuromuscular blockade whether anesthesia is maintained with propofol or sevoflurane. After administration of sugammadex 4.0 and 8.0 mg/kg at a PTC of 1–2, the time to recovery of the T_4/T_1 ratio to 0.9 averaged 3.3 and 1.5 min, respectively, under propofol anesthesia⁸ and 1.7 and 1.1 min under sevoflurane in this study. These findings agree with those of Vanacker et al.,¹⁰ who observed that recovery from moderate rocuronium-induced neuromuscular blockade after sugammadex was unaffected by the kind of maintenance anesthesia. Nevertheless, in this study, sugammadex was administered at a median time after initiation of sevoflurane of 49 min in the rocuronium group and 41 min in the vecuronium group (and 1 patient did not receive maintenance sevoflurane anesthesia until 47 min after sugammadex administration), and it cannot be discounted that a longer exposure time to sevoflurane before administration of sugammadex may have led to different results.

Table 4. Description of Reoccurrence of Blockade in the 5 Patients in the Rocuronium Group

| Dose (mg/kg) | Maximum T_4/T_1 ratio reached before reoccurrence | | Minimum T_4/T_1 ratio during reoccurrence | | Time after sugammadex of eventual recovery of the T_4/T_1 ratio to 0.9 (min) |
|------------------|---|-----------------------------|---|-----------------------------|--|
| | T_4/T_1 ratio | Time after sugammadex (min) | T_4/T_1 ratio | Time after sugammadex (min) | |
| 1 | >0.9 | 3.6 (time to TOF 0.9) | 0.61 | 37.1 | Not reached during monitoring |
| 1 | >0.9 | 7.4 (time to TOF 0.9) | 0.60 | 71.2 | |
| 0.5 ^a | 0.65 | 4.9 | 0.27 | 17.4 | 61.6 |
| 0.5 ^b | 0.83 | 11.5 | 0.70 | 41.3 | 88.3 |
| 1 | 0.82 | 8.1 | 0.68 | 32.6 | 91.4 |

TOF = train-of-four.

^a Patient described in the publication by Eleveld et al.¹²

^b TOF trace for this patient shown in Figure 2.

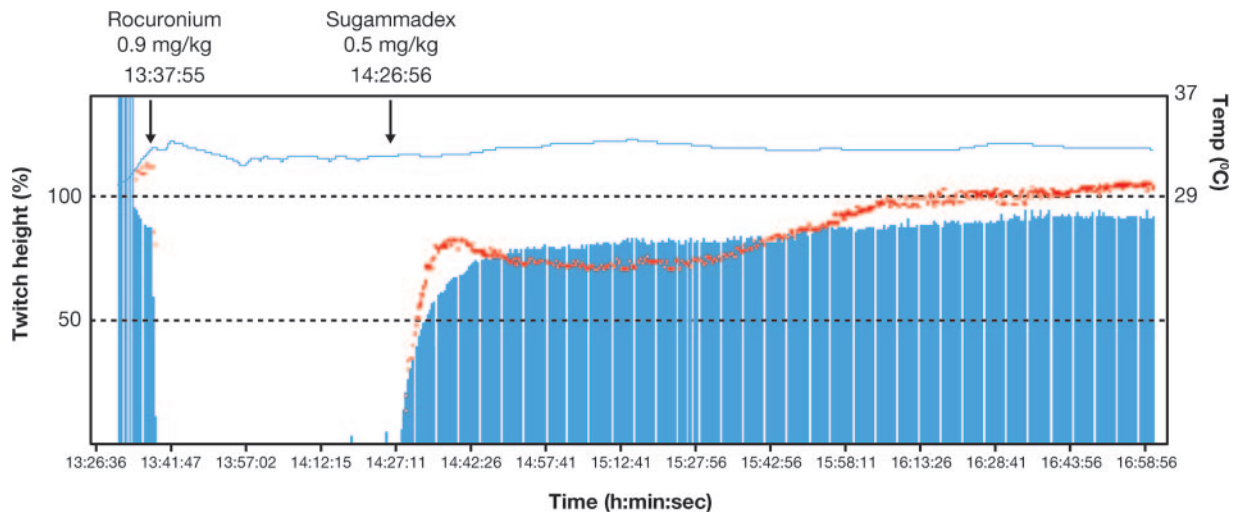


Figure 2. Representative train-of-four trace from a patient who experienced recurrence of blockade after administration of a low dose of sugammadex (0.5 mg/kg) at a target of 1–2 posttetanic counts after rocuronium 0.9 mg/kg.

Our study also suggests that sugammadex is effective for the reversal of deep vecuronium-induced neuromuscular blockade. Although this is the first published study to show the efficacy of sugammadex in this setting (i.e., deep vecuronium-induced blockade), another study reported that sugammadex was effective for the reversal of moderate (0.1 mg/kg) vecuronium-induced neuromuscular blockade, with a mean time to recovery of the T_4/T_1 ratio to 0.9 of 1.5 min after administration of sugammadex 4.0 mg/kg.³ Similar recovery times were observed after sugammadex reversal of deep neuromuscular blockade induced by vecuronium as with rocuronium.

These results highlight the positive attributes of sugammadex at reversing deep neuromuscular blockade in comparison with the acetylcholinesterase inhibitors, which are ineffective in this role.¹⁶ This difference is attributable to their mechanisms of action. Sugammadex acts by binding to either rocuronium or vecuronium, which results in a rapid decrease in their free concentration in plasma and at the target sites, the nicotinic receptors on motor endplates.^{1,4} As the NMBD becomes less available to bind with the nicotinic receptors, it is liberated from the receptors and normal muscle activity is reinstated. In contrast, acetylcholinesterase inhibitors have no effect on the concentration of either rocuronium or vecuronium, because they act by increasing the half-life of acetylcholine and, therefore, its concentration at the neuromuscular junction on the surface of muscle fibers. As a result, they are effective at reversing moderate but not deep neuromuscular blockade.^{2,17}

For 4 subjects only, SAEs were reported during this study, none of which were considered by the investigators to be related to sugammadex. This reflects a good tolerability profile for sugammadex, which, along with the apparent plateau of recovery attained in both NMBD groups, is supported further by results of other clinical studies with sugammadex.^{3,5–10,18,19}

Although recurrence of blockade was observed with neuromuscular monitoring in 5 patients after sugammadex administration in the rocuronium group, no patients who were tracheally extubated after acquiring a TOF value of 0.9 had clinical evidence of recurrent or residual neuromuscular blockade as assessed by clinical tests and measurements of oxygen saturation and breathing frequency. The reported incidents of recurrent neuromuscular blockade in the rocuronium group all occurred in patients who had received low doses of sugammadex (0.5 mg/kg, $n = 2$; 1.0 mg/kg, $n = 3$), which were shown to be suboptimal for reversal of the depth of block (i.e., deep block at 1–2 PTCs) investigated in this study (Table 2). One patient in the rocuronium group (sugammadex 1.0 mg/kg) had an AE that was based on TOF values and coded by the investigator as “neuromuscular block prolonged.” To explain the effect of suboptimal doses, Eleveld et al.¹² speculated that, although the sugammadex dose in the central compartment may be sufficient for complex formation with NMBD molecules, it could be insufficient in the peripheral compartment, thus unbound NMBD molecules could redistribute into the central compartment resulting in a temporary increase in muscle relaxation intensity.

CONCLUSIONS

This study suggests that sugammadex at doses of ≥ 4 mg/kg provides rapid reversal of deep rocuronium- and vecuronium-induced neuromuscular blockade in surgical patients under sevoflurane maintenance anesthesia. Sugammadex was found to be generally well tolerated in the surgical patients included in this study.

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The Influence of Endotoxemia on the Electroencephalographic and Antinociceptive Effects of Isoflurane in a Swine Model

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BACKGROUND: We have previously reported that hemorrhagic shock decreases the minimum alveolar anesthetic concentration (MAC) of isoflurane but minimally alters the electroencephalographic (EEG) effect. In this study, we investigated the influence of endotoxemia on the EEG effect and the MAC of isoflurane.

METHODS: Eighteen swine (25.7 ± 2.3 kg) were anesthetized by inhalation of isoflurane. The inhaled concentration was decreased to 0.5% and maintained for 20 min, before being returned to 2% and maintained for a further 20 min. End-tidal isoflurane concentrations and spectral edge frequencies were recorded. Analysis of the pharmacodynamics was performed using a sigmoidal inhibitory maximal effect model for spectral edge frequencies versus effect-site concentration. After measurement of the EEG effect, MAC was determined using the dewclaw clamp technique in which movement in response to clamping is recorded. After completion of control measurements, infusion of lipopolysaccharide (LPS, $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was started after a 100- μg bolus administration. After 1 h, the inhaled concentration of isoflurane was varied as in the control period, and the MAC was assessed again (LPS1h). The same procedures were also performed after 3 h of LPS infusion (LPS3h).

RESULTS: Endotoxemia decreased the effect-site concentration that produced 50% of the maximal effect from $1.31\% \pm 0.22\%$ to $1.13\% \pm 0.14\%$ (LPS1h) and $1.03\% \pm 0.22\%$ (LPS3h) and decreased the MAC from $2.05\% \pm 0.20\%$ to $1.51\% \pm 0.30\%$ (LPS1h) and $1.21\% \pm 0.29\%$ (LPS3h).

CONCLUSIONS: Endotoxemia increases both the hypnotic and antinociceptive effects of isoflurane, in contrast to hemorrhagic shock, and the extent of these alterations increases with progression of endotoxemia.

(Anesth Analg 2010;110:83-8)

Hemorrhagic shock increases the effect of several classes of IV anesthetics because of an increase in drug concentration induced by a reduction in the distribution volume and clearance and an increase in end-organ sensitivity.¹⁻⁵ In contrast, inhaled anesthetics have different pharmacokinetic properties. Uptake from alveoli to blood is restricted by blood solubility (blood/gas partition coefficient) and cardiac output (CO), and the drug concentration does not exceed the vaporizer setting. Furthermore, only a small amount of an inhaled anesthetic is metabolized and most is

eliminated through exhalation. These properties suggest that an increase in drug effect due to pharmacokinetic changes will not occur for inhaled anesthetics, even during hemorrhagic shock. We have previously examined the influence of hemorrhagic shock on the electroencephalographic (EEG) effect of isoflurane in a swine model and concluded that hemorrhage minimally alters the EEG effect of isoflurane, even at a level at which hemorrhagic shock progresses to a decompensated state.^{6,7} These results suggest that use of an inhaled anesthetic, rather than an IV anesthetic, may allow for easier control of the hypnotic state in patients with significant perioperative blood loss.

Endotoxemia also increases the hypnotic effect of IV anesthetics,⁸⁻¹⁰ but results from hemorrhagic shock studies cannot be applied to septic shock because these forms of shock differ pathophysiologically. Sepsis or systemic inflammatory response syndrome induces encephalopathy, which is characterized by acute reversible decreases in cerebral function varying from impaired mental function with changes in vigilance, disorientation, sleepiness, and deep coma.¹¹ Therefore, it is possible that endotoxemia will increase the hypnotic effect of inhaled anesthetics, in contrast to hemorrhagic shock.

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This study was performed to investigate the influence of endotoxemia on the hypnotic effect of isoflurane. As in our previous studies of hemorrhagic shock, we assessed changes in the spectral edge frequency (SEF) and end-tidal isoflurane concentration (EtIso) between 0.5% and 2% inhaled concentrations, with induction of endotoxemia by continuous infusion of lipopolysaccharide (LPS) in a swine model. The minimum alveolar anesthetic concentration (MAC) was also assessed to allow a comparison of the hypnotic and antinociceptive effects. We hypothesized that endotoxemia would alter both the hypnotic and antinociceptive effects of isoflurane.

METHODS

Animal Preparation

The study was approved by the Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan. Eighteen pigs (body weight range: 20.0–29.3 kg, mean \pm SD = 25.7 \pm 2.3 kg) were used in the study. General anesthesia was induced by isoflurane inhalation (5%) in oxygen at 6 L/min using a standard animal mask. After tracheostomy, the lungs of the pigs were mechanically ventilated, and anesthesia was maintained with a 2% inhaled concentration of isoflurane in an oxygen-air mixture (oxygen/air = 3:3 L/min). Expiratory gases were analyzed using a Capnomac Ultima (ULT-V-31-04, Datex-Ohmeda, Helsinki, Finland) throughout the study. The ventilator was adjusted to keep the end-tidal carbon dioxide between 35 and 45 mm Hg during the preparation period, and this setting was maintained throughout the study. Lead II of an electrocardiogram was monitored using 3 cutaneous electrodes. A pulmonary artery catheter (5F, 4 lumen, Nihon Kohden, Tokyo, Japan) and a central venous catheter (16 gauge) were inserted via the right jugular vein, and another catheter (16 gauge) was placed in the right femoral artery. The blood temperature was measured using the pulmonary artery catheter and maintained between 39.0°C and 39.5°C (normothermia for pig). After these preparatory steps, EEG monitoring was started by preparing the skin over the frontooccipital regions bilaterally and positioning 4 cutaneous electrodes (Zipprep, Aspect Medical Systems, Natick, MA). Four channels of the electroencephalogram were amplified and digitally recorded using an Aspect A-1000 EEG instrument with version 3.0 software (Aspect Medical Systems). The low-pass and high-pass filters were set at 0.2 and 70 Hz, respectively. Processed EEG values were collected electronically at intervals of 10 s.

Experimental Protocol

After completion of animal preparation, baseline measurements were taken after a further 30 min, and then the inhaled isoflurane concentration was decreased from 2% to 0.5% and maintained at this level

for 20 min, before being returned to 2% and maintained at this level for a further 20 min for EEG measurement of the hypnotic effect. After measurement of the EEG effect, MAC was assessed beginning at a 2% end-tidal concentration. After determination of MAC under control conditions, the inhaled isoflurane concentration was returned to 2%, and 100 μ g of LPS (LPS from *Escherichia coli*, O127:B8, Sigma-Aldrich, St. Louis, MO) was administered via a central venous catheter. LPS was then administered continuously at a rate of 1 μ g \cdot kg⁻¹ \cdot h⁻¹ with an infusion pump until the end of the study. After 1 h (LPS1h condition), and after confirming the stability of the electroencephalogram, the inhaled isoflurane concentration was decreased from 2% to 0.5% and maintained at this level for 20 min, before being returned to 2% and maintained at this level for a further 20 min for evaluation of the hypnotic effect, in a similar manner to the procedure under control conditions. After measurement of the EEG effect, MAC was assessed again. These procedures were also performed after 3 h of LPS administration (LPS3h condition) to examine whether the severity of endotoxemia influenced the extent of alterations in variables. Metabolic variables were measured before measurement of the EEG effect in each condition. Heart rate (HR), mean arterial blood pressure (MAP), mean pulmonary arterial pressure (MPAP), central venous pressure, and CO were recorded at each inhaled concentration (the first 2%, 0.5%, and the second 2% of isoflurane) during measurement of the EEG effect for each condition (control, LPS1h, and LPS3h). CO was determined with a thermodilution computer (Cardiac Output Computer, MTC6210, Nihon Kohden) using 5 mL of cold 5% glucose injected into the right atrium.

Pharmacodynamic Analysis of the Hypnotic Effect

The hypnotic effect of isoflurane was characterized by examining the influence of isoflurane on the SEF (the 95th percentile of the power distribution), as described previously.^{6,7,12} The SEF is related to the effect-site concentration (C_e), which is derived from the classic first-order decay of the EtIso: $dC_e/dt = k_{e0}(EtIso - C_e)$, where k_{e0} is the elimination constant from the effect-site and determines the equilibrium between EtIso and C_e . The k_{e0} value was calculated for each animal using the nonlinear least-squares fitting method in Microsoft Excel 2000 (Microsoft, Redmond, WA). Optimization of k_{e0} was accomplished using the Solver tool in Excel by minimizing the area bounded by the hysteresis loop plotted between the SEF values every 10 s and the EtIso values at the respective times. Because plots of the concentration-EEG effect relationship were sigmoidal, an inhibitory sigmoid E_{max} equation (Hill equation)¹³ was used to model the relationship parametrically. The following equation, $E = E_0 - (E_0 - E_{max}) \times [C_e^\gamma / (C_e^\gamma + EC_{50}^\gamma)]$, was used, in which E is the predicted effect, E_0 is the baseline effect, E_{max} is the maximal effect, EC_{50} is the C_e that

produces 50% of the maximal effect, and γ is a measure of curve steepness, which was used to fit the equation to data for an individual animal. The parameters in the model were estimated using nonlinear least-squares fitting in Excel, through optimization with the Solver tool to minimize the sum of squares between the estimated and measured SEF values. We also report the coefficient of determination (R^2) as an objective function,¹⁴ as described previously.^{6,7,12}

Determination of MAC

MAC was assessed under control conditions and at 2 stages of LPS administration in each animal, starting from a 2% end-tidal concentration of isoflurane. The starting value was determined with reference to the MAC value found in our previous reports.^{15,16} A supramaximal pain stimulus was created by application of a clamp to the dewclaw for 60 s, and the presence or absence of a withdrawal reaction during the 60-s period was recorded. A positive reaction was defined either as a withdrawal of the clamped foot or as a gross movement of another leg or the head. If a positive response occurred, the end-tidal concentration was increased by 0.2%. In exceptional cases in which a positive response occurred but hemodynamic changes were minimal, the end-tidal concentration was increased by 0.1%. After another equilibration period of 20 min, a second noxious stimulus was applied, and this protocol was repeated until no motor reaction occurred. If no motor response was elicited by the noxious stimulus, the end-tidal concentration was decreased by 0.2%. In exceptional cases in which no motor response was elicited but hemodynamic changes were large, the end-tidal concentration was decreased by 0.1%, and the protocol was repeated until a movement response occurred. The study protocol was considered complete after a change in movement response from positive to negative or *vice versa*. MAC was calculated as the average of the highest isoflurane concentration at which movement occurred and the lowest concentration at which movement was suppressed.

Statistical Analysis

Data are expressed as means \pm SD. Hemodynamic variables at each inhaled concentration during EEG measurements and differences in metabolic and pharmacodynamic variables and MAC for each condition were analyzed using repeated-measures 1-way analysis of variance. If the analysis of variance indicated significance, a Scheffé *F*-test for multiple comparisons was performed. *P* values <0.05 were considered to be statistically significant.

RESULTS

In the experiments, progression of hypotension was followed by ventricular fibrillation. Three pigs died before 1 h during LPS infusion and 1 died after the measurements in the LPS1h condition (before the

Table 1. Hemodynamic Variables in Each State

| | Control (n = 18) | LPS1h (n = 15) | LPS3h (n = 14) |
|-------------------------------|----------------------------|-----------------------------|-----------------------------|
| HR 2% (bpm) | 121 \pm 12 | 158 \pm 27 ^a | 188 \pm 38 ^b |
| HR 0.5% (bpm) | 159 \pm 26 ^c | 196 \pm 34 ^{ad} | 216 \pm 46 ^{ac} |
| HR 2% _{o2} (bpm) | 132 \pm 15 | 184 \pm 36 ^{ad} | 193 \pm 38 ^a |
| MAP 2% (mm Hg) | 63 \pm 6 | 53 \pm 8 ^a | 55 \pm 13 ^a |
| MAP 0.5% (mm Hg) | 91 \pm 11 ^c | 73 \pm 16 ^{ac} | 77 \pm 16 ^{ac} |
| MAP 2% _{o2} (mm Hg) | 70 \pm 11 | 56 \pm 8 ^a | 59 \pm 13 ^a |
| MPAP 2% (mm Hg) | 16 \pm 2.8 | 22 \pm 4.4 ^a | 27 \pm 5.2 ^b |
| MPAP 0.5% (mm Hg) | 18 \pm 2.5 | 24 \pm 4.6 ^{ad} | 29 \pm 5.9 ^{bd} |
| MPAP 2% _{o2} (mm Hg) | 16 \pm 2.5 | 26 \pm 5.7 ^{ad} | 28 \pm 5.4 ^a |
| CVP 2% (mm Hg) | 4.6 \pm 1.8 | 3.4 \pm 1.6 ^a | 3.3 \pm 1.9 ^a |
| CVP 0.5% (mm Hg) | 3.8 \pm 1.8 ^d | 3.0 \pm 1.5 | 3.2 \pm 2.4 |
| CVP 2% _{o2} (mm Hg) | 3.8 \pm 1.7 ^d | 3.2 \pm 1.6 | 3.3 \pm 1.9 |
| CO 2% (L/min) | 3.0 \pm 0.4 | 2.3 \pm 0.4 ^a | 1.8 \pm 0.5 ^b |
| CO 0.5% (L/min) | 3.5 \pm 0.7 ^c | 2.4 \pm 0.6 ^{ae} | 1.9 \pm 0.6 ^{be} |
| CO 2% _{o2} (L/min) | 2.9 \pm 0.4 | 2.2 \pm 0.4 ^a | 1.7 \pm 0.5 ^b |

Data are expressed as mean values \pm SD.

LPS = lipopolysaccharide; CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial blood pressure; MPAP = mean pulmonary arterial pressure; CO 2%, CVP 2%, HR 2%, MAP 2%, and MPAP 2% = CO, CVP, HR, MAP, and MPAP at the first inhaled isoflurane concentration of 2%, respectively; CO 0.5%, CVP 0.5%, HR 0.5%, MAP 0.5%, and MPAP 0.5% = CO, CVP, HR, MAP, and MPAP at an inhaled isoflurane concentration of 0.5%, respectively; CO 2%_{o2}, CVP 2%_{o2}, HR 2%_{o2}, MAP 2%_{o2}, and MPAP 2%_{o2} = CO, CVP, HR, MAP, and MPAP at the second inhaled isoflurane concentration of 2%, respectively.

^a Significant difference versus control.

^b Significant differences versus control and LPS1h.

^c Significant differences versus both 2% states.

^d Significant difference versus the first 2% state.

^e Significant difference versus the second 2% state.

Table 2. Metabolic Variables in Each State

| | Control (n = 18) | LPS1h (n = 15) | LPS3h (n = 14) |
|--------------------------|---------------------|-----------------------------|-----------------------------|
| pH | 7.50 \pm 0.03 | 7.51 \pm 0.04 | 7.47 \pm 0.06 |
| pCO ₂ (mm Hg) | 37.4 \pm 4.9 | 31.3 \pm 3.7 ^a | 28.7 \pm 4.3 ^a |
| pO ₂ (mm Hg) | 232 \pm 40 | 273 \pm 57 ^a | 272 \pm 41 ^a |
| Base excess (mM) | 5.6 \pm 2.4 | 2.4 \pm 2.9 ^a | -1.2 \pm 3.5 ^b |
| Lactate (mM) | 2.4 \pm 1.1 | 2.8 \pm 0.9 | 4.7 \pm 2.0 ^b |
| Hematocrit (%) | 28.9 \pm 2.8 | 35.8 \pm 2.6 ^a | 40.4 \pm 4.0 ^b |

Data are expressed as mean values \pm SD.

LPS = lipopolysaccharide.

^a Significant difference versus control.

^b Significant differences versus control and LPS1h.

LPS3h measurements). Hemodynamic variables at each isoflurane concentration during EEG measurements and metabolic variables in each condition are shown in Tables 1 and 2, respectively. Endotoxemia increased HR and MPAP and decreased MAP and CO, and the changes in HR, MPAP, and CO increased with progression of endotoxemia. All hemodynamic variables except central venous pressure tended to increase at 0.5% isoflurane and returned to baseline values with restoration of 2% isoflurane. LPS infusion decreased base excess and increased hematocrit and lactate.

A plot of SEF values against EtI_{so} showed hysteresis in all animals, as previously reported.^{6,7,12} The hysteresis was collapsed by estimating the elimination constant from the effect-site (k_{e0}), resulting in the

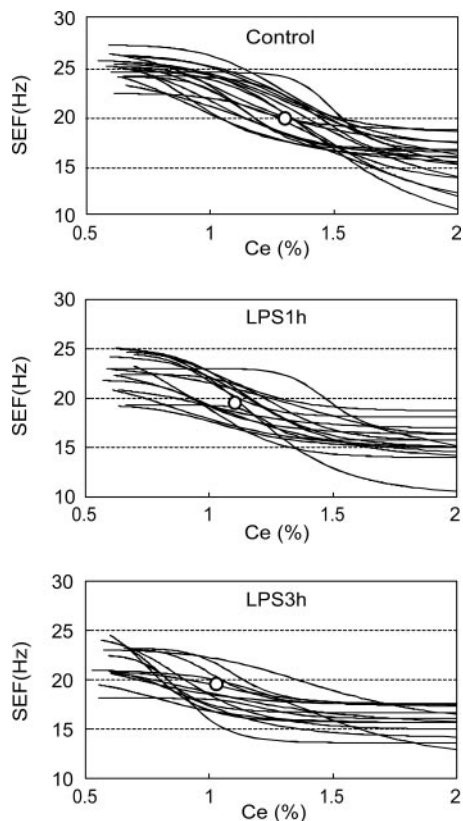


Figure 1. Individual relationships between spectral edge frequency (SEF) and effect-site isoflurane concentration (C_e) under control conditions and after lipopolysaccharide (LPS) administration for 1 and 3 h. Open circles are mean EC_{50} values.

Table 3. Pharmacodynamic Variables for the Hypnotic Effect

| | Control (<i>n</i> = 18) | LPS1h (<i>n</i> = 15) | LPS3h (<i>n</i> = 14) |
|------------------|-----------------------------|---------------------------|---------------------------|
| k_{e0} (1/min) | 0.68 ± 0.18 | 0.48 ± 0.23^a | 0.43 ± 0.20^a |
| E_0 (Hz) | 25.1 ± 1.1 | 22.7 ± 2.1^a | 22.2 ± 2.0^a |
| E_{max} (Hz) | 14.2 ± 3.8 | 15.4 ± 2.1 | 15.6 ± 1.7 |
| γ | 7.5 ± 3.5 | 11.1 ± 9.4 | 7.6 ± 3.0 |
| EC_{50} (%) | 1.31 ± 0.22 | 1.13 ± 0.14^a | 1.03 ± 0.22^a |

Data are expressed as mean values \pm sd.

LPS = lipopolysaccharide; E_0 = baseline spectral edge effect level; E_{max} = maximal spectral edge effect; EC_{50} = effect-site concentration that produces 50% of the maximal spectral edge effect; γ = a measure of curve steepness; k_{e0} = elimination constant from the effect site.

^a Significant difference versus control.

C_e -SEF effect relationship for isoflurane. The individual curves for all animals in 3 states are shown in Figure 1. The correlation coefficients (R^2) between the SEF and the C_e were 0.94 ± 0.03 under control conditions, 0.87 ± 0.11 at LPS1h, and 0.81 ± 0.14 at LPS3h. Endotoxemia significantly shifted the concentration-effect relationship to the left. The EC_{50} (the C_e that produces 50% of the maximal SEF effect) values were 1.31 ± 0.22 under control conditions, 1.13 ± 0.14 at LPS1h ($P = 0.03$ versus control), and 1.03 ± 0.22 at LPS3h ($P < 0.01$ versus control). The pharmacodynamic variables are presented in Table 3. Endotoxemia decreased k_{e0} , E_0 , and EC_{50} , but other pharmacodynamic variables did not change.

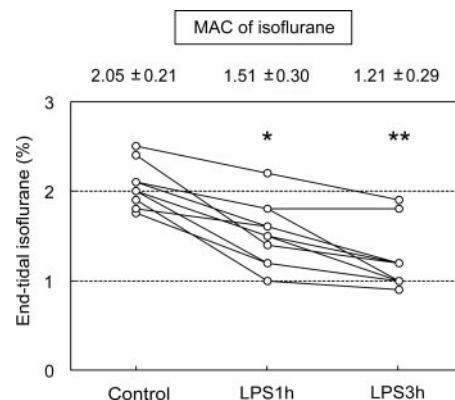


Figure 2. Minimum alveolar anesthetic concentration (MAC) of isoflurane under control conditions and after lipopolysaccharide (LPS) administration for 1 and 3 h in each animal. Data are expressed as mean values \pm sd. *Significant difference versus control. **Significant difference versus control and LPS1h.

MAC values for each condition are shown in Figure 2. MAC decreased under LPS infusion in all swine. The mean MAC values were $2.05\% \pm 0.21\%$ under control conditions, $1.51\% \pm 0.30\%$ at LPS1h ($P < 0.01$ versus control), and $1.21\% \pm 0.29\%$ at LPS3h ($P < 0.01$ versus control and LPS1h), indicating that the MAC of isoflurane decreases with progression of endotoxemia.

DISCUSSION

Our results show that endotoxemia alters the EEG effect and the MAC of isoflurane, indicating that endotoxemia increases the hypnotic and antinociceptive effects of isoflurane. The extent of these changes increased with progression of the severity of endotoxemia. To our knowledge, this is the first study to demonstrate an influence of endotoxemia on the hypnotic effect of an inhaled anesthetic. In addition to the pharmacodynamic changes, alterations in the pharmacokinetics of coadministered drugs induced by the significant decrease in CO with progression of endotoxemia may also contribute to an anesthetic-sparing effect during general anesthesia in septic patients.

Lipsey et al.¹⁷ have examined the relationships of the endotoxin dose and administration period with inflammatory, coagulatory, and hemodynamic responses (tumor necrosis factor- α , interleukin-6, white blood cell count, platelet count, MAP, MPAP, cardiac index, oxygen delivery, mixed venous oxygen saturation, hemoglobin, base excess, and dynamic pulmonary compliance) in anesthetized pigs, with administration of LPS IV for 6 h at doses of 0.063, 0.25, 1, 4, 8, and $16 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in each animal. Most variables were found to change within 3 h after the start of LPS infusion and dose-dependent deteriorations in these variables were observed, with some pigs that received a dose of $>1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ dying after 3 h.¹⁷ On the basis of these findings, we used $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ continuous infusion after a $100\text{-}\mu\text{g}$ bolus dose and evaluated the influence of endotoxemia on the effect of

isoflurane at 1 and 3 h after LPS infusion. We found that hemodynamic and metabolic variables after 3 h of LPS infusion deteriorated compared with those after 1 h, and this allowed evaluation of the influence of endotoxemia on the potency of isoflurane at 2 different stages of severity of endotoxemia. The results indicated that progression of endotoxemia influences the extent of pharmacodynamic alterations.

Several reports have shown that sepsis decreases the MAC of inhaled anesthetics,^{18–20} consistent with our findings. Allaouchiche et al.^{18,19} demonstrated decreases in the MAC of sevoflurane and desflurane to 44% and 27%, respectively, in a normotensive septic pig model, and Gill et al.²⁰ showed that sepsis decreased the MAC of isoflurane to 43% in a normotensive septic rat model. However, the underlying mechanism is unclear. Because previous studies have examined the MAC while maintaining a normotensive and normovolemic hemodynamic status, the decrease in MAC cannot be attributable to global hemodynamic depression. We have recently reported that hemorrhagic shock decreases the MAC of isoflurane to an extent that is correlated with the severity of the shock and that the decrease in MAC is not reversed by fluid resuscitation but by administration of naloxone, which suggests that endogenous opioids are involved in the decrease in MAC.¹⁶ Molina²¹ showed marked increase of the plasma β -endorphin level in animals after soft tissue trauma and LPS administration, similar to the effects of hemorrhage. Therefore, we speculate that alteration of MAC values might at least partially be attributable to endogenous opioids induced under various stress conditions.

Endotoxemia increases the hypnotic effect of propofol and midazolam.^{8–10} De Paepe et al.¹ have examined the influence of endotoxemia on the pharmacokinetics and the EEG effect of propofol in rats and demonstrated a reduction of almost 50% in the propofol dose needed to reach the EEG end point in endotoxin-treated rats. The predicted C_e at the return of the righting reflex was lower in these rats, but because EC_{50} assessed by electroencephalography did not differ significantly, it was concluded that the increase in the propofol effect was mainly attributable to an increase in drug concentration induced by a reduction in the distribution volume and clearance. Previous reports have shown a decrease in the anesthetic requirement of IV anesthetics during endotoxemia, but the hypnotic effect of inhaled anesthetics has not been studied.

We have previously examined the influence of hemorrhagic shock on the EEG effect of isoflurane in a swine model and concluded that hemorrhage minimally alters the EEG effect of isoflurane, even at a level at which hemorrhagic shock progresses to a decompensated state,^{6,7} although hemorrhagic shock clearly decreases the MAC.¹⁶ The antinociceptive effect increases in hemorrhagic shock and endotoxemia,

but different results are observed regarding the hypnotic effect: endotoxins cause encephalopathy, in contrast to hemorrhagic shock. In clinical practice, septic encephalopathy is often the first manifestation of sepsis²² and has been reported to occur in 70% of septic patients²³; however, this condition tends to be underdiagnosed because many critically ill patients receive treatment such as sedation, mechanical ventilation, or neuromuscular junction blockade that masks the signs of neural dysfunction. Patients with septic encephalopathy show impaired attention, orientation, concentration, and writing, and (in more severe cases) delirium and coma.¹¹ The etiology of septic encephalopathy involves reduced cerebral blood flow and oxygen extraction by the brain, cerebral edema, disruption of the blood-brain barrier that may arise from the action of inflammatory mediators on the cerebrovascular endothelium, abnormal neurotransmitter composition of the reticular activation system, impaired astrocyte function, and neuronal degeneration.²⁴ In particular, the reticular activation system controls consciousness and attention, and damage to this system might increase the hypnotic effect of isoflurane. Several studies have demonstrated that the electroencephalogram and sensory evoked potentials can be used to evaluate the incidence and severity of septic encephalopathy,^{25–27} although there are no clear criteria. Young et al.²⁵ have demonstrated that the electroencephalogram is a useful index of brain function in septic encephalopathy. The EEG changes are correlated with the severity of encephalopathy, which results in a quantitative EEG shift to slower waves with a dominance of δ and an association with interspersed triphasic waves or unspecific suppression patterns. In the clinical setting, processed EEG data are frequently used rather than raw EEG results to evaluate the hypnotic depth, especially during anesthesia, and in this study, endotoxemia significantly increased the EEG effect of isoflurane assessed by SEF. From these findings, we speculate that the increase in the hypnotic effect during endotoxemia is probably attributable to septic encephalopathy, and that an increase in the hypnotic effect of an inhaled anesthetic during anesthesia in septic patients might suggest the occurrence of septic encephalopathy.

Some limitations of this study need to be addressed. A time-control study of the measurements of SEF and MAC in the absence of LPS was not performed, and it is especially possible that repetitive noxious stimuli during MAC assessment might influence subsequent evaluation of SEF and MAC. In addition, EEG measurements were not performed in an awake condition in the study, although electroencephalography might be useful for indicating the occurrence of septic encephalopathy. However, it is difficult to perform EEG measurements under an awake condition without anesthetics in pigs from both technical and ethical perspectives.

In conclusion, endotoxemia increases both the hypnotic and antinociceptive effects of isoflurane. These results differ from our previous findings for hemorrhagic shock, in which the hypnotic effect was minimally altered even in a decompensated hemorrhagic shock state. Care should be taken in extrapolating results from animal studies to clinical practice, but our results suggest that the anesthetic requirement for an inhaled anesthetic may be reduced during general anesthesia in septic patients.

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The Effect of Preoperative Heart Rate and Anxiety on the Propofol Dose Required for Loss of Consciousness

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BACKGROUND: Conflicting results have been reported on the effect of anxiety on the propofol dose required for inducing loss of consciousness (LOC). The hemodynamic effects of anxiety, increased heart rate (HR), and cardiac output may account for these discrepancies. We therefore designed this study to address, first, the effect of perioperative HR on propofol dose required for LOC and, second, the effect of perioperative anxiety on HR.

METHODS: Forty-five ASA physical status I–II female patients undergoing gynecological surgery were studied. Anxiety was assessed in the operating room with the State-Trait Anxiety Inventory (STAI)-state Spielberger scale (situational anxiety). After HR recording, anesthesia was induced with a 200-mL/h 1% propofol infusion with the Base Primea® pump (Fresenius-Vial, Brezins, France) until LOC. The propofol dose was recorded at the time of LOC. Relationships between STAI-state and HR versus propofol dose at LOC were tested with the Spearman test with a *P* value of 0.01.

RESULTS: A significant relationship was observed between HR and propofol dose at LOC ($\rho = 0.487$, $P = 0.0012$) but not between STAI-state and propofol dose ($\rho = 0.330$, $P = 0.0306$). However, a significant relationship was observed between STAI-state and HR ($\rho = 0.462$ and $P = 0.0054$).

CONCLUSION: Increased perioperative HR is associated with increased propofol dose required for LOC. Perioperative anxiety accounts for increased HR.

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Anxiety is a frequent patient concern during the perioperative period. Apart from compromising patients' well-being, it may affect induction of anesthesia. As suggested by clinical experience, the more anxious the patient, the higher the hypnotic dose required for induction of anesthesia (propofol being the hypnotic drug most frequently investigated).^{1,2} However, this assumption has been recently challenged.³

Some studies that investigated the effects of perioperative anxiety recorded the propofol dose required to obtain loss of consciousness (LOC) or a defined level of sedation^{1,2} but did not consider the hemodynamic effects of anxiety. Anxiety and acute mental stress are associated with increased heart rate (HR) and cardiac output.^{4–8} Because hemodynamic status during induction of anesthesia may modify propofol requirements for LOC,^{9–12} we hypothesized that HR before induction of anesthesia may affect propofol dose requirements for

LOC and that anxiety before induction of anesthesia may influence HR. Although intuitive, this latter relationship has not been previously demonstrated in the immediate preinduction setting.

We therefore designed this study to address, first, the effect of perioperative HR on the propofol dose required for LOC and, second, the effect of perioperative anxiety on HR.

METHODS

The study was conducted between June 2007 and February 2008. It was approved by the Ethics Committee of Cochin Hospital, Assistance Publique-Hôpitaux de Paris. Written informed consent was obtained from each patient.

Patients

Consecutive female patients, 18–65 yr old, ASA physical status I or II, undergoing scheduled gynecological surgery were approached to participate in the study. Exclusion criteria were as follows: pregnancy; neurologic or psychiatric disease; chronic medication with β -blockers, anxiolytics, antidepressants, or opioids; documented alcohol or drug abuse; or inability to complete the anxiety forms.

Assessment of Anxiety

Anxiety was assessed with the Spielberger's State-Trait Anxiety Inventory (STAI) form.¹³ This is a validated tool for self-reporting anxiety, already used

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during the perioperative period.^{1-3,14} It comprises 2 sets of 20 statements.

The first set relates to the immediate situation, the state anxiety. It includes statements such as "I feel calm" or "I am worried." For each statement, the patient is required to select 1 of 4 responses: not at all, somewhat, moderately so, or very much so. To the best of our knowledge, there is no published cutoff value of the STAI-state score discriminating the anxious from nonanxious patient.

The second set of statements is intended to reflect underlying long-term or trait anxiety. Examples include "I feel pleasant" or "I am a steady person." Again, the subject is required to select a single response: almost never, sometimes, often, or all the time.

A score for each set, ranging between 20 and 80, may then be calculated by an investigator using a scoring key. Higher scores indicate higher anxiety. The score for the STAI-trait set does not change as the context changes, contrary to the score for the STAI-state. It takes about 10 min to complete both forms.

The patients were asked to complete the 2 STAI forms (state and trait) on the morning of surgery, while waiting in their room in the surgical ward and the STAI-state form in the operating room, immediately before induction of anesthesia.

Assessment of HR and Induction of Anesthesia

No preanesthetic medication was given on the morning of surgery. On arrival in the operating room, a 20-gauge IV catheter was inserted in the left hand. A 3-way stopcock was connected to the catheter and devoted to propofol infusion. Intravenous lidocaine to decrease pain caused by propofol infusion was forbidden. For perioperative warming, a forced-air blanket (Bair Hugger®, Arizant, Eden Prairie, MN) was used because it may affect STAI results.¹⁴ Patients were monitored with noninvasive arterial blood pressure, 5-lead electrocardiogram, and pulse oximetry.

Once the patient had completed the STAI-state form in the operating room, HR and systolic blood pressure (SBP) were measured. HR and SBP values used for further analysis were the mean of 3 consecutive measurements.

Anesthesia was induced with a continuous 200-mL/h 1% propofol infusion (AstraZeneca, Rueil-Malmaison, France) with the Base Primea® pump (Fresenius-Vial, Brezins, France) until LOC, defined as loss of verbal contact. Loss of verbal contact was tested every 15 s from the start of propofol infusion by asking the patient, in a normal voice but without tactile stimulation, to say her name. Until LOC, the airway was managed with a facemask but without jaw thrust to avoid patient stimulation. The same investigator identified when LOC occurred and inserted a mark in the Rugloop® (Demed Company, Temse, Belgium) recording. The investigator was blinded to the STAI form results. The software running the pump allowed for real-time calculation of propofol effect-site concentrations (Ce) according to the pharmacokinetic model of Schnider et al.¹⁵

This model considers patient's age, sex, and lean body mass. The propofol dose and Ce were continuously recorded until LOC and stored on a personal computer with Rugloop software (<http://www.demed.be>). After LOC, the continuous infusion was switched to a Ce target-controlled infusion, and the study was terminated.

Rugloop files were analyzed *a posteriori*. LOC was identified through the mark inserted in the operating room. Predicted Ce and propofol dose at the time of LOC were retrieved.

Statistical Analysis

Results are presented as median (interquartile range; range). The associations between STAI-trait, STAI-state in the ward and in the operating room, HR and SBP versus dose, and Ce at the time of LOC were studied with the Spearman test. A *P* value <0.01 was considered statistically significant because 5 associations were tested for dose and Ce. Associations with a *P* value <0.05 were entered into a multiple regression analysis. Analysis was conducted with StatView software (SAS Institute, Cary, NC).

For comparison of STAI-state measured in the ward and in the operating room, we used a Wilcoxon test, and concordance between the 2 values was measured with the concordance correlation coefficient. A *P* value <0.05 was considered statistically significant. Analysis was conducted with StatView software (SAS Institute).

For calculation of the sample size, we used a method for studies involving linear regression because all the variables tested were continuous quantitative variables. Our main hypothesis was to demonstrate a significant relationship between HR (the *x* axis or independent variable) in the operating room and propofol dose for LOC (the *y* axis or dependent variable). With the method described by Dupont and Plummer,¹⁶ calculation requires knowing the SD of the *x* variable (HR) and the *y* variable (propofol dose), which was obtained for the first 20 patients included in the study (78 ± 15 per minute and 116 ± 25 mg, respectively), and to select an α and β risk (0.05 and 0.20, respectively). In addition, you must define what the expected regression coefficient between the *x* and *y* variables may be. We chose a 0.5 value according to Kazama,¹⁷ who studied the determinants of propofol induction dose requirements expressed in milligram with a methodology similar to ours. He obtained correlation coefficients between 0.4 and 0.6. Therefore, we selected the intermediate value of 0.5. With the aforementioned values, 34 patients had to be included (PS-Power and sample size calculation software).¹⁶

RESULTS

Forty-five patients were enrolled. Their characteristics are presented in Table 1. One patient was not able to complete the STAI-state form in the operating room because of a panic attack.

Table 1. Characteristics of the 45 Patients

| | |
|---|-----------------------------|
| Age (yr) | 39 (25–47; 20–61) |
| Height (cm) | 165 (160–169; 150–177) |
| Weight (kg) | 62 (55–74; 47–100) |
| Body mass index (kg/m ²) | 23.4 (19.6–26.6; 17.7–36.7) |
| STAI-trait on the morning of surgery | 39 (33–42; 25–56) |
| STAI-state on the morning of surgery | 42 (33–50; 24–73) |
| STAI-state in the operating room | 42 (33–49; 20–68)* |
| Systolic blood pressure in the operating room (mm Hg) | 123 (116–136; 100–190) |
| Heart rate in the operating room (bpm) | 78 (64–88; 51–126) |

One patient was not able to complete the STAI-state questionnaire in the operating room. Data are presented as median (interquartile range; range).

STAI = State-Trait Anxiety Inventory.

* Not statistically different from STAI-state on the morning of surgery ($P = 0.1478$ with Wilcoxon test; concordance correlation coefficient = 0.8077).

Table 2. Association Between STAI-Trait, STAI-State, Heart Rate (HR), and Systolic Blood Pressure (SBP) and Propofol Dose, Propofol and Predicted Effect Site Concentration (Ce) at the Time of Loss of Consciousness (LOC)

| | Propofol dose | Propofol Ce |
|--------------------------------------|--------------------------------|--------------------------------|
| STAI-trait on the morning of surgery | $P = 0.596$ $\rho = 0.08$ | $P = 0.886$ $\rho = 0.022$ |
| STAI-state on the morning of surgery | $P = 0.0317$ $\rho = 0.324$ | $P = 0.0251$ $\rho = 0.338$ |
| STAI-state in the OR | $P = 0.0306$ $\rho = 0.330$ | $P = 0.0229$ $\rho = 0.347$ |
| SBP in the OR (mm Hg) | $P = 0.4191$ $\rho = 0.122$ | $P = 0.548$ $\rho = 0.091$ |
| HR in the OR (bpm) | $P = 0.0012$ $\rho = 0.487$ | $P = 0.0003$ $\rho = 0.542$ |

STAI = State-Trait Anxiety Inventory; OR = operating room.

$P < 0.01$ considered statistically significant.

The time that elapsed between the 2 STAI-state forms was 3 h (1–5 h; range: 0.5–22 h). No difference was observed between the score obtained for the STAI-state assessment in the ward and in the operating room (Table 1). Upon LOC, the propofol dose was 107 mg (97–128 mg; range: 79–183 mg), and the predicted Ce was 4.8 $\mu\text{g}/\text{mL}$ (4.4–5.3 $\mu\text{g}/\text{mL}$; range: 3.5–6.7 $\mu\text{g}/\text{mL}$).

On the morning of surgery, no significant correlation was observed between STAI-state (situational anxiety) and propofol dose for LOC and between STAI-trait (proneness to anxiety) and propofol dose (Table 2). Similar results were observed with Ce.

In the operating room, no significant correlation was observed between STAI-state (situational anxiety) and propofol dose required for LOC (Table 2). Similar results were observed with Ce. A significant relationship was observed between HR and propofol dose at LOC but not between SBP and propofol dose (Table 2). Similar results were observed with Ce. In multiple regression, analyzing the effect of STAI-state in the operating room and HR in the operating room on propofol dose and Ce at LOC, only HR was significant

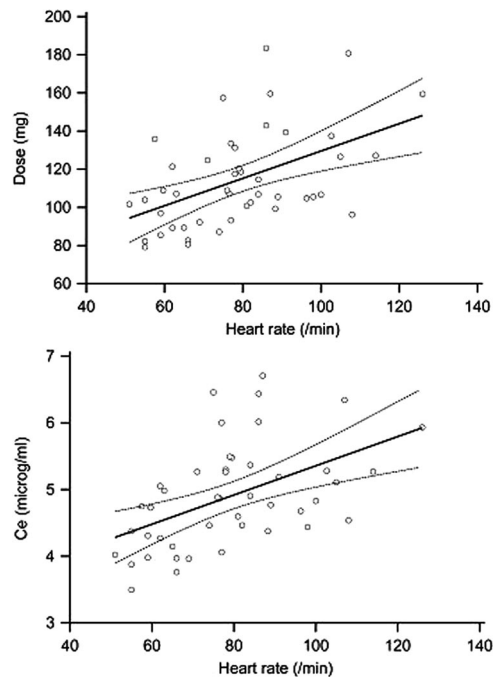


Figure 1. Relationship between heart rate in the operating room and propofol dose (top; $\rho = 0.487$ and $P = 0.0012$) and between heart rate in the operating room and predicted effect-site concentration (bottom; $\rho = 0.542$ and $P = 0.0003$). Curved dotted lines are the 95% confidence intervals.

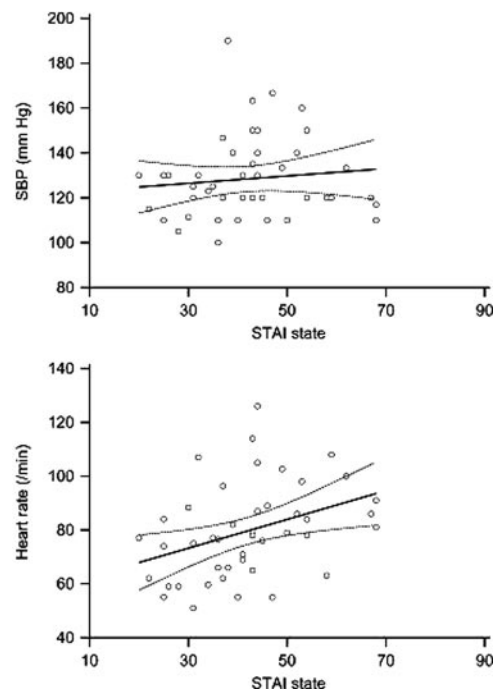


Figure 2. Relationship between State-Trait Anxiety Inventory (STAI)-state in the operating room and systolic blood pressure (SBP) (top; $\rho = 0.181$ and $P = 0.2364$) and between STAI-state in the operating room and heart rate (bottom; $\rho = 0.462$ and $P = 0.0024$). Curved dotted lines are the 95% confidence intervals.

($P = 0.0011$ for propofol dose and $P = 0.0021$ for propofol Ce) (Fig. 1). In the operating room, a significant relationship was observed between STAI-state and HR but not between STAI-state and SBP (Fig. 2).

DISCUSSION

Of the variables we investigated, HR recorded just before starting the propofol infusion was the only predictor of propofol dose or Ce for LOC in multiple regression analysis. This is in agreement with the results of Morley et al.,³ who also demonstrated a significant relationship between preinduction HR and the propofol dose required for loss of verbal response or to obtain a bispectral index (BIS) value of 50.

However, our results do not exclude an effect of anxiety on propofol dose or Ce but rather support an indirect effect. We observed a strong relationship between STAI-state in the operating room and HR, i.e., the more anxious the patient, the more rapid the HR. Although intuitive, this relationship has not been demonstrated in the immediate preinduction setting. Anxiety is associated with an increase in both HR and cardiac output.⁴⁻⁷ Similarly, acute mental stress, as would be expected in the operating room, is also responsible for increased HR and cardiac output.⁸ Anxiety and stress-induced adrenaline release may account for this hemodynamic pattern as suggested by Fell et al.¹⁸ However, anxiety is only one of the determinants of HR; anemia, dehydration, or other perioperative factors that we did not control for in this study may influence it. Conflicting results have been reported in the 3 published studies concerning the effects of anxiety on propofol dose for producing a defined end point.¹⁻³ Maranets and Kain¹ reported that increased STAI-trait but not STAI-state on the day of surgery was associated with higher propofol dose administered as a bolus to achieve a BIS value between 40 and 60. Similarly, Hong et al.² reported that increased anxiety assessed by a visual analogic scale but not by the STAI scale on the day of surgery was associated with higher propofol dose administered with a target-controlled infusion to reach a predetermined level of sedation. On the contrary, Morley et al.³ did not observe any influence of the STAI-trait and STAI-state measured in the surgical ward and propofol dose administered at a $40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ infusion rate to achieve LOC or a BIS value of 50. In this study, we did not observe a relationship between state and trait anxiety measured in the ward and in the operating room and propofol dose or Ce for LOC and suggest that the effect of anxiety on propofol dose is probably an indirect one, related to HR changes. However, we cannot exclude a type 1 error, i.e., an underpowered study, because the calculation of the sample size relied only on the demonstration of a significant relationship between HR in the operating room and propofol dose and did not consider the multiple comparisons we made. This hypothesis is suggested by the trend toward statistical significance we observed between STAI-state in the ward and in the operating room and propofol dose, with *P* values between 0.01 and 0.05. Apart from an effect of HR, the depth of anesthesia used as an end point may be

responsible for the discrepancies observed among studies because the hemodynamic effect of anxiety, and probably cardiac output, may disappear as the anesthesia level deepens, reducing the dose discrepancies in anxiety states. In this study, we chose LOC as our clinical end point because it is the commonly accepted clinical end point used in many clinical investigations of the effects of hypnotic drugs.^{12,15,19} Furthermore, studying loss of responsiveness to a noxious stimulus such as laryngoscopy or tracheal intubation, which is of more clinical interest to the anesthesiologist, would have entailed the coadministration of opioids and made analysis of the results more complex. Apart from a pharmacologic mechanism, selection of the end point and propofol infusion rate may induce a measurement error. The error of dose can be relatively high if a bolus of propofol is given because LOC is assessed clinically at intervals of several seconds. We chose to administer a slow continuous infusion to minimize error. If a target BIS value is chosen as the end point for depth of anesthesia, this introduces several other potential sources of error. First, BIS is calculated from the raw electroencephalogram with a lag time of 30–45 s.²⁰ The BIS value upon LOC probably underestimates the true level of depth of anesthesia and may explain why BIS values at LOC are high in many studies. Second, if a low BIS value is the end point as in the studies by Maranets and Kain¹ and Morley et al.,³ this is associated with another potential source of error because the relationship between propofol dose and BIS value may not be linear. Taking into consideration the aforementioned sources of error, we estimate that the method associated with the lowest risk of error is the one we used: continuous propofol infusion and LOC estimation every 15 s.

Lack of arterial propofol concentration²¹ and of cardiac output measurements in our study makes it difficult to evaluate mechanisms responsible for the increased propofol dose required when HR, and probably anxiety, increase. In other words, it is not possible from the current data to determine whether the increased requirements are related to a pharmacokinetic or a pharmacodynamic change. Previous studies have demonstrated that hemodynamic status, especially cardiac output, modifies propofol requirements.⁹⁻¹² Because there is a good relationship between HR and cardiac output in healthy patients but not between SBP and cardiac output, our results suggest that increased propofol requirements for LOC when HR increases are related to increased cardiac output.²² This assumption may be further supported by the effect of preanesthetic medication with β -blockers on propofol requirements.²³

The model by Schnider et al.¹⁵ used to predict propofol Ce concentration from infused propofol dose considers patient age, weight, sex, and height. Because the model does not consider the hemodynamic status, i.e., HR, values obtained in this study should be accepted with caution. Although we studied healthy

patients and tried to decrease the variability of the pharmacokinetic model^{24,25} and the inaccuracy of estimated propofol Ce concentration during the first minute of infusion²⁶ with a slow infusion rate for inducing anesthesia (200 mL/min), we cannot be certain of the accuracy of the predicted Ce in this study.

This study was an explanatory study and did not intend to draw practical considerations, i.e., dose or target selection for inducing anesthesia. However, the wide variability of both propofol dose (range: 79–183 mg) and predicted Ce (3.5–6.7 µg/mL) highlights that the best dose or concentration choice for induction of anesthesia should be based on the individual titration of dose or concentration using a clinical end point for titrating. This titration is of particular importance during induction because the hemodynamic effect of anxiety, and probably cardiac output, may fade as the anesthesia level deepens.

Because all the variables tested in this study were continuous quantitative variables (propofol dose, propofol Ce, anxiety scores, HR, and SBP), we decided to use a regression analysis. We could have used 2 groups of patients for our analysis but that would imply separating the patients into anxious versus nonanxious with an arbitrary cutoff value that could not be defined from the published data.

In conclusion, increased perioperative HR is responsible for increased propofol dose required for LOC. Perioperative situational anxiety accounts for increased HR and propofol requirement.

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Pressures Available for Transtracheal Jet Ventilation from Anesthesia Machines and Wall-Mounted Oxygen Flowmeters

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BACKGROUND: Oxygen supplies capable of supporting transtracheal jet ventilators can be lifesaving. There is not much information about which oxygen sources (readily available inside and outside operating rooms) have sufficient driving pressure for transtracheal jet ventilation.

METHODS: We measured driving pressures (upstream or residual oxygen pressure) in a specially designed jet ventilation test system with a 2.25-mm (14-gauge) IV catheter. High-pressure oxygen sources evaluated included wall-mounted (Puritan, Allied Health, Precision, and Datex-Ohmeda) and anesthesia machine auxiliary oxygen flowmeters and oxygen flush valves from anesthesia machines (Draeger Narkomed 2B, Narkomed 4, Datex-Ohmeda Excel, and Datex-Ohmeda Modulus).

RESULTS: All 4 types of wall-mounted oxygen flowmeters, opened past their highest scale settings (15 L/min), delivered sufficient working pressures (range, 103–282 kPa; 16–41 psi). Working pressures from auxiliary oxygen flowmeters mounted on Datex-Ohmeda machines were adequate to support jet ventilation (range, 189–248 kPa; 27–36 psi), whereas those on tested Draeger machines did not supply sufficient pressure for jet ventilation: Narkomed 2B, 14–28 kPa (2–4 psi); Narkomed 4, 24–28 kPa (3–4 psi). Working pressures delivered by oxygen flush valves on tested Draeger machines were adequate to support jet ventilation, ranging from 96 to 117 kPa (14–17 psi), whereas pressures generated by tested Datex-Ohmeda flush valves were not (ranging from 50 to 62 kPa, 7–9 psi).

CONCLUSION: Oxygen sources other than dedicated jet ventilator connectors to high-pressure pipeline oxygen may supply adequate working pressure, but each type of oxygen source needs testing to ensure that it supplies adequate working pressure.

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During emergency management of patients with difficult airways, the availability and use of jet ventilation through a transtracheal catheter can be lifesaving.^{1,2} The inability to provide life-sustaining gas exchange under circumstances in which neither ventilation by mask nor intubation can be achieved has been responsible for up to 30% of deaths attributed to anesthesia.^{3–5} Currently available commercial jet ventilators require a connection to a high-pressure oxygen supply, for instance, on some anesthesia machines in which connectors are readily available. Thus, a jet ventilator and personnel instructed in its use will often not be available when airway emergencies in patients

with unexpected difficult airways occur outside the operating room (OR). We therefore investigated the utility of wall-mounted oxygen flowmeters as a source of oxygen pressure for jet ventilation compared with oxygen flush valves found on anesthesia machines, which have been shown to be satisfactory.⁶

The static oxygen pipeline pressure* provided in hospitals in the United States is about 378 kPa (55 psi).⁷ During use for jet ventilation, this pressure will decrease. The pressure of interest is the residual or working pressure† available for jet ventilation through a 2.25-mm (14-gauge) IV catheter. This is the actual pressure driving oxygen through the 2.25-mm (14-gauge) catheter into the patient, for which we use the term “working pressure.” Commercially available jet ventilators include pressure regulators specifically designed to reduce the dangerously high pipeline pressure to safer but effective levels. Although pressure must be reduced

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*Static oxygen pipeline pressure refers to the pipeline pressure while no oxygen is flowing.

†Residual pressure (or working pressure) refers to upstream driving pressure remaining while oxygen is flowing through the 14-gauge cannula. We accepted, based on the literature, a minimum working pressure of 103 kPa (15 psi) as the minimum pressure required to drive the jet ventilator (see Discussion).

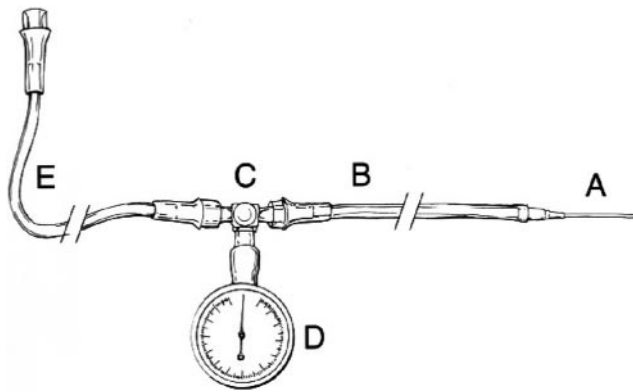


Figure 1. The specially designed, constant flow test assembly used to measure the “working pressure” (driving pressure while jet ventilator is fully open to atmosphere). A, 2.25-mm (14-gauge) IV catheter; B and E, airline oxygen tubing; C, Hi-Flo 3-Way Stopcock; D, oil-filled pressure gauge.

to reduce the chance of injury, the working pressure should be at least 103 kPa (15 psi) to drive sufficient oxygen through a 14-gauge catheter.

The purpose of this study was to measure the pressures available for jet ventilation from the oxygen sources with anesthesia machines and from several types of wall-mounted oxygen outlets, as found in the postanesthesia care unit, emergency room, surgical intensive care unit (SICU), medical intensive care unit, and the general wards in a typical hospital. A complete list of the working pressures available to drive oxygen through a 2.25-mm (14-gauge) IV catheter from these sources has not been published. We examined which oxygen sources could be used with a 2.25-mm (14-gauge) catheter for transtracheal jet ventilation.

METHODS

The measurement technique called for a test system to provide a constant flow of oxygen through a 2.25-mm (14-gauge) catheter rather than the standard jet ventilation devices that are designed for intermittent flow. The measurement technique also had to consider the decrease in available pipeline pressure caused by the flow of oxygen; as soon as flow occurs, the supply pressure decreases to a new, lower level (“working pressure”), which represents the balance between the inflow and outflow. On the basis of the literature, we accepted 103 kPa (15 psi) as the minimum pressure required for jet ventilation.

Therefore, to enable measurement of the working pressures during continuous use of the test jet ventilator system, we assembled equipment in the following sequence (test assembly) for our measurements (Fig. 1):

1. 2.25-mm (14-gauge) 56.7-mm Jelco™ IV catheter (4068, 0294G84, Critikon, 1748C, Tampa, FL)
2. 2.1-m Airline Oxygen tubing, vinyl-tipped (Lot No. YOCO262, Cat. 001301, Allegiance, McGaw Park, IL)

3. Hi-Flo 3-Way Stopcock (24D22076, MX 931-IL, Medex, Hilliard, OH)
4. 2.1-m Airline Oxygen tubing (as in item 2)
5. Standard 7-mm endotracheal tube connector (Intermediate Hi-Lo, Cat. #86450, Lot M041150, MMJ S.A. de C.V., Mexico, G.P. 32580) to connect test system to the common gas outlet of the anesthesia machine. The tubing (as in item 4) connected directly to the wall-mounted oxygen flowmeters (without the need for a coupling piece)
6. Connecting tubing connected to third opening of 3-Way Stopcock (as in item 3, 5-mm internal diameter; 20-cm length)
7. Oil-filled pressure gauge with a range of 0 to 413 kPa (0–60 psi) connected to 7 (WIKA, Lawrenceville, GA)

We connected the test assembly in turn to each of the following oxygen sources:

1. Anesthesia machines:
 - a. Datex-Ohmeda Modulus and Datex-Ohmeda Excel (Datex-Ohmeda, The BOC Group, Madison, WI)
 - b. Narkomed 2B and Narkomed 4 (North American Draeger, Telford, PA)
 - i. to the common gas outlet of each anesthesia machine
 - ii. to the auxiliary oxygen flowmeter of each anesthesia machine
2. Wall-mounted oxygen flowmeters:
 - a. Allied Health (TL 015 Model, Allied Health Instrument Corp., St. Louis, MO)
 - b. Precision (IMFA 1001, Precision Medical, Northampton, PA)
 - c. Datex-Ohmeda (AHE, BOC Health Care, Columbia, MD)
 - d. Puritan (Series B, no manufacturer details available).

We first determined the influence of 6 identical (from the same manufacturer) 2.25-mm (14-gauge) IV catheters on the working pressures from a single source (Datex-Ohmeda wall-mounted oxygen flowmeter) during jet ventilation to check for variability. Because the variability of the pressures was only minimal and not clinically relevant when using different catheters of the same size, we continued the testing with a single 2.25-mm (14-gauge) IV catheter.

The following anesthesia machines were used for our measurements: Narkomed 2B, Narkomed 4, Datex-Ohmeda Modulus, and Datex-Ohmeda Excel. These machines were in different locations (main OR, labor and delivery OR, outpatient OR, and spare machines) and tested on different days. The machine type, serial number, service date, vaporizer, and further available information were documented. The oxygen pipeline pressures for the different locations and days were documented before and during the measurements.

We connected the test equipment to the common gas outlet of the anesthesia machine and pressed and held the emergency oxygen button on the anesthesia machine. We read the pressure on the pressure gauge. Air could be heard and felt escaping between the body of the vaporizer and the rotating head of the Draeger anesthesia machines. We examined each vaporizer to determine which vaporizer "leaked." Every measurement was repeated 5 times. All available anesthesia machines in our institution were studied using the above protocol.

Four different types of wall-mounted oxygen flowmeters (Datex-Ohmeda, Allied Health, Puritan, and Precision) at different locations (pediatric and adult postanesthesia care unit, surgical intensive care unit, trauma bay, emergency room, and floor) at the Hershey Medical Center were tested on different days. Flowmeter manufacturers, types, and serial numbers were noted where available. The oxygen pipeline pressures for the different locations and days were documented before and during the experiments. The oxygen pipelines were all parts of the clinical hospital system and maintained as per standard regulations.

We also tested the auxiliary oxygen flowmeters mounted on the anesthesia machines. The flow ranges of the flowmeters were 0–10 L/min for the Draeger anesthesia machines and 0–15 L/min for the Datex-Ohmeda anesthesia machines. The steps of the pressure measurements for the oxygen flowmeters mounted on the anesthesia machines and the wall were made as follows:

1. Wall pressure (oxygen supply pressure) was noted (with no oxygen flowing).
2. Flowmeter was opened to obtain its highest flow setting according to the calibrated scale (10 or 15 L/min), with no back pressure (i.e., jet ventilator not connected).
3. Test measurement system was connected.
4. Pressure reading on the oil-filled pressure gauge of the test assembly was noted.
5. New (lower) reading on the oxygen flowmeter (L/min) was noted (but not reported).
6. Flowmeter was opened further, past the highest flowmeter scale setting.⁷ All the flowmeters had a definite, clear "stop," past which it was not possible to open the device any further.
7. Pressure reading on the oil-filled pressure gauge was noted while the oxygen was flowing through the 2.25-mm (14-gauge) IV catheter (this is the working pressure, as defined previously).
8. Because the flowmeter bobbin was past (higher than) the highest setting on the scale, no flow reading could be obtained on the auxiliary oxygen flowmeter.
9. Wall pressure ("working pressure") was noted during the flow of oxygen.

Every pressure measurement was repeated 5 times for each flowmeter. Six different flowmeters of each brand were tested. The means, standard deviations, and ranges were calculated for each individual flowmeter. The averages of each of the 6 different flowmeters were used to calculate (and report) the mean and standard deviations for each group of flowmeters. Pressures were measured in psi and converted to kPa using a conversion factor of 0.145.

Commercial Jet ventilators

Using a similar methodology, we tested 3 commercially available jet ventilators (AINCA, Anesthesia Associates, San Marcos, CA, Cat. #00-325):

As a baseline measurement, we measured the working pressures with the commercial devices connected in the conventional format directly to a high-pressure oxygen source.

As a comparative measurement, we measured the working pressures provided to the commercial devices by each of the wall-mounted oxygen flowmeters mentioned above.

The serial numbers of all tested devices are provided in the Appendix.

RESULTS

Variability Because of IV Catheters

When using 6 different 2.25-mm (14-gauge) IV catheters with the highest scale setting on the flowmeter, the working pressures measured during jet ventilation were 28 kPa (4 psi) with minimal variation. The working pressure for a totally open setting (maximum possible flow setting with the flowmeter opened wider than the highest calibrated/rated setting) was 234 kPa (34 psi), also with minimal variation. Because the measurements for the highest scale setting and for the totally open setting showed only minimal variability, we considered the differences between catheters to be not clinically relevant.

Anesthesia Machine Common Gas Outlet (Oxygen Flush Valve)

All tested machines were in current use and serviced within the previous 3 months as per clinical requirements. We tested 15 Narkomed 2B machines, 3 Narkomed 4 machines, 3 Datex-Ohmeda Modulus machines, and 1 Datex-Ohmeda Excel machine. The pipeline oxygen pressures varied between 372 and 392 kPa (54–57 psi) during our measurements. The pressure measurements obtained from the oxygen flush valves ranged from 96 to 117 kPa (14–17 psi) with a mean of 102 kPa (14.8 psi) for the Narkomed 2B machines; from 96 to 103 kPa (14–15 psi) with a mean of 99 kPa (14.3 psi) for the Narkomed 4 machines; from 50 to 55 kPa (7.2–8 psi) for the Datex-Ohmeda Modulus machines with a mean of 52 kPa (7.6 psi); and all 5 readings were 62 kPa (9 psi) for the Datex-Ohmeda Excel machine (Table 1).

Table 1. Working Pressures Obtained with Different Anesthesia Machines Using the Oxygen Flush Valve as the Source of High-Pressure Oxygen Flow

| Anesthesia machine | N | Static wall pressure in kPa (mean ± SD) | Working pressure in kPa (mean ± SD) |
|----------------------|----|--|--|
| Narkomed 2B | 15 | 376 ± 11 | 102 ± 66 |
| Narkomed 4 | 3 | 372 | 99 ± 4 |
| Datex Ohmeda Modulus | 3 | 386 ± 6 | 52 ± 7 |
| Datex Ohmeda Excel | 1 | 372 | 62 |

N is the number of each type of anesthesia machine tested. Static wall pressure in kPa is the pressure read on the anesthesia machine pressure gauge without any oxygen flow. Working pressure is the pressure measured upstream of the 2.25-mm (14 gauge) IV catheter, connected to the anesthesia machine circuit while using the oxygen flush valve. Mean is the average pressure.

Table 2. Working Pressures Obtained with Auxiliary Flow Meters of Different Anesthesia Machines

| Auxiliary flowmeter type | N | Wall pressure in kPa (mean ± SD) | Working pressure in kPa (mean ± SD) |
|--------------------------|----|-------------------------------------|--|
| Narkomed 2B | 15 | | |
| HSS | | 374 ± 9 | 19 ± 5 |
| TOS | | | 27 ± 5 |
| Narkomed 4 | 3 | | |
| HSS | | 372 | 14 ± 2 |
| TOS | | | 25 ± 2 |
| Datex Ohmeda Modulus | 3 | | |
| HSS | | 377 ± 4 | 33 ± 5 |
| TOS | | | 239 ± 8 |
| Datex Ohmeda Excel | 1 | | |
| HSS | | 392 | 34 |
| TOS | | 392 | 190 |

N is the total number of anesthesia machines tested, wall pressure in kPa is the pressure read on the anesthesia machine pressure gauge without any oxygen flow, and the working pressure is the pressure measured upstream to the 2.25-mm (14 gauge) IV catheter, connected to the anesthesia machine flowmeter. HSS is with the control valve open to allow oxygen flow (L/min) set to the flowmeter's maximum number in L/min on its scale (10 L/min for Draeger machines, 15 L/min for Datex Ohmeda machines) and TOS maximum is with the control valve open completely, allowing maximum possible oxygen flow through the flowmeter.

HSS = highest scale setting; TOS = totally open setting.

With the Draeger anesthesia machines, we noted that with the use of the oxygen flush valve, gas escaped from underneath the head of the vaporizer even though the vaporizer was closed. There was no consistent pattern in which vaporizers leaked: the first, second, or last in sequence; most recently used or opened; or type of vaporizer (halothane, enflurane, isoflurane, or sevoflurane). Despite the audible leak, the residual working pressures were still sufficient (i.e., >103 kPa; Table 1.) As expected (based on the design), at no stage did any of the desflurane vaporizers leak. None of the Datex-Ohmeda anesthesia machines had a leak from the vaporizer during activation of the oxygen flush button.

Anesthesia Machine Auxiliary Flowmeters

The working pressures obtained from the auxiliary flowmeters on the Narkomed anesthesia machines (15 of Narkomed 2B and 3 of Narkomed 4) varied from 14 to 28 kPa (2–4 psi) while set at the highest scale flow (10 L/min). This working pressure did not increase sufficiently (i.e., remained significantly <103 kPa), even when set on the maximum possible flows (Table 2).

Table 3. Working Pressures Measured from Different Wall-Mounted Oxygen Flow Meters

| Type of wall-mounted oxygen flowmeter | N | Wall pressure in kPa (mean ± SD) | Working pressure in kPa (mean ± SD) |
|---------------------------------------|---|-------------------------------------|--|
| Puritan | 6 | | |
| HSS | | 383 ± 6 | 29 ± 4 |
| TOS | | | 147 ± 41 |
| Timeter | 6 | | |
| HSS | | 381 ± 3 | 34 ± 2 |
| TOS | | | 267 ± 6 |
| Precision | 6 | | |
| HSS | | 379 | 29 ± 2 |
| TOS | | | 252 ± 21 |
| Ohmeda | 6 | | |
| HSS | | 383 ± 6 | 30 ± 4 |
| TOS | | | 257 ± 11 |

N is the total number of flowmeters tested, wall pressure in kPa is the pressure read on the anesthesia machine pressure gauge without any oxygen flow. The working pressure is the pressure measured upstream to the 2.25-mm (14 gauge) intravenous catheter, connected to the anesthesia machine flowmeter. HSS is with the control valve open to allow oxygen flow (L/min) set to the flowmeter rated highest number in L/min on its scale (15 L/min for wall-mounted oxygen flowmeters). TOS is with the control valve open completely, allowing maximum possible oxygen flow through the flowmeter.

HSS = highest scale setting; TOS = totally open setting.

The working pressures, measured with the auxiliary oxygen flowmeters on the 3 Datex-Ohmeda Modulus anesthesia machines, varied from 28 to 38 kPa (4–5.5 psi) at the highest flow according to the flowmeter scales (15 L/min) and ranged from 231 to 248 kPa (33.5–36 psi) (Table 2) while set on the maximum possible flow.

The 5 working pressures, measured with the oxygen flowmeter on the single Datex-Ohmeda Excel anesthesia machine, all read 34 kPa (5 psi) at the highest flow according to the flowmeter scales (15 L/min) and ranged from 189 to 193 kPa (27.5–28 psi) (Table 2).

Wall-Mounted Oxygen Flowmeters

The working pressure measurements obtained from the wall-mounted oxygen flowmeters varied from 24 to 34 kPa (3.5–5 psi) at the highest flow setting of the flowmeters (15 L/min) and ranged from 100 to 282 kPa (14.5–41 psi) while set at the maximum possible flow (Table 3). The working pressures (measured at maximum possible flow) tended to be the lowest (but still sufficient) with the Puritan flowmeters. The Puritan flowmeter pressures varied from 100

Table 4. Working Pressures Measured from 3 Commercially Available Jet Ventilators with Auxiliary Flowmeter from Draeger Anesthesia Machine 6400 and Different Wall-Mounted Oxygen Flowmeters

| Type of device | Wall pressure in kPa (mean) | Working pressure in kPa (mean ± SD) |
|---------------------------------|-----------------------------|-------------------------------------|
| Draeger anesthesia machine 6400 | 372 | |
| Auxiliary flowmeter | | |
| HSS | | 5 ± 7 |
| TOS | | 7 ± 6 |
| Oxygen flush valve | | 2 ± 3 |
| Puritan | | |
| HSS | 324 | 28 ± 14 |
| TOS | | 120 ± 38 |
| Timeter | | |
| HSS | 326 | 28 ± 21 |
| TOS | | 179 ± 50 |
| Precision | | |
| HSS | 324 | 21 ± 12 |
| TOS | | 168 ± 51 |
| Ohmeda | | |
| HSS | 323 | 30 ± 21 |
| TOS | | 184 ± 49 |

Three commercially available jet ventilators (AINCA, Anesthesia Associates, San Marcos, CA) were tested. Wall pressure in kPa is the pressure read on the control or anesthesia machine pressure gauge without any oxygen flow. The working pressure is the pressure measured upstream to the 2.25-mm (14 gauge) IV catheter, connected to the analogue pressure gauge on the jet ventilator. The mean is the average working pressure. HSS is with the control valve open to allow oxygen flow (L/min) set to the flowmeter rated highest number in L/min on its scale (15 L/min for wall-mounted oxygen flowmeters). TOS is with the control valve open completely, allowing maximum possible oxygen flow through the flowmeter.

HSS = highest scale setting; TOS = totally open setting.

to 172 kPa (14.5–25 psi) with a mean of 147 kPa (21.3 psi) (Table 3).

Commercially Available Jet Ventilators

The “static” wall oxygen pressures (i.e., without oxygen flow) obtained from the control panel, and the pressure gauge from the anesthesia machine, varied from 323 to 372 kPa (47–54 psi). The working pressures provided by a conventional high-pressure oxygen source, directly connected to the commercial jet ventilator, varied from 179 to 283 kPa (26–41 psi). The working pressures for the wall-mounted oxygen flowmeters were all sufficient (i.e., >103 kPa), whereas the working pressures for the Draeger anesthesia machine’s auxiliary flowmeter were insufficient (Table 4).

DISCUSSION

Because jet ventilation is not needed very often, it is not economical or feasible to have dedicated oxygen outlets for commercial jet ventilators at every location where jet ventilation might be required. Although there can be life-threatening complications with jet ventilation,^{8,9} it can, however, be lifesaving during attempts to establish an adequate airway.^{10,11}

We were interested in determining whether jet ventilation could be used outside the OR environment and whether sufficient working pressures could be obtained using equipment readily available outside the OR, such as oxygen flowmeters. Furthermore, we

tested whether the anesthesia machines available in our clinical environment could act as a “high-pressure oxygen source” at sufficiently high pressures to drive a jet ventilator. We defined a high-pressure oxygen source as a pressure in the range of wall (pipeline) supply pressure and above. We also compared our results with published data.

Oxygen Flush Valves

Published literature on working pressures necessary for transtracheal jet ventilation systems suggest that the oxygen flush valves of some anesthesia machines supply sufficient working pressure for jet ventilation.³ Gaughan et al.⁶ studied the Draeger Narkomed 2, 2A, 2B, and 3 anesthesia machines, as well as the Datex-Ohmeda Modulus II, Modulus II Plus, and the Datex-Ohmeda Modulus CD anesthesia machines. They concluded that the working pressures of the Draeger Narkomed 2A, 2B, and 3 anesthesia machines, as well as of the Datex-Ohmeda Modulus II Plus and the Datex-Ohmeda Modulus CD anesthesia machines, supplied sufficient pressure (124 kPa or 18 psi) to give adequate tidal volumes for jet ventilation in model lungs. However, according to their study, the Draeger Narkomed 2 and the Datex-Ohmeda Modulus II did not supply adequate working pressures from the oxygen flush valve. Bould and Bearfield¹² measured the flow achieved through a transtracheal catheter and compared their device (“construction”) to a Manujet jet ventilator and to a Sanders injector for emergency ventilation. This “construction” (as they termed their homemade device) consisted of a standard hospital wall oxygen supply, flowmeter, oxygen tubing, and a 3-way tap. They found that this system was appropriate for emergency use in the absence of a jet ventilator.

Zornow et al.¹³ performed an animal study using 3 different systems for jet ventilation. They were able to document sufficient ventilation and oxygenation using a jet ventilator attached to the oxygen pipeline and the flush valve of the anesthesia machine. Histological examinations of the tracheas, after using 345-kPa (50-psi) sources for the jet ventilation, demonstrated tracheal injuries, and they concluded that lower pressures of 103–206 kPa (15–30 psi), as used by Lawler et al.,¹⁴ may minimize these injuries. On the basis of these studies, we considered working pressures of approximately 103 kPa or more (15 psi) as sufficient for jet ventilation. Where we had comparable measurements, the working pressures observed during our measurements using the oxygen flush valve on anesthesia machines were consistent with the data obtained by Gaughan et al.⁶ Therefore, our measurements now expand this database: we consider the working pressures produced by the Narkomed 4 as sufficient and the Datex-Ohmeda Excel flush valve pressures as insufficient for jet ventilation (Table 1).

The idea for this study originated when, during training sessions for simulated airway emergencies in

the Simulation Development and Cognitive Science Laboratory of the Pennsylvania State University College of Medicine, we noted that oxygen flowmeters could produce much higher flows than the maximum flow rate printed on the flow scale. This is evident when opening auxiliary flowmeters to the maximum scale setting and then continuing to open the control valves. This observation led us to evaluate the pressures available for jet ventilation, at such higher flows, using the auxiliary oxygen flowmeters of anesthesia machines as well as wall-mounted oxygen flowmeters at other hospital locations. We must explicitly indicate that the use of oxygen flowmeters (wall-mounted or on anesthesia machines) above their stated upper limit is not approved by the Food and Drug Administration or supported by the manufacturers.

Auxiliary Oxygen Flowmeters

During tests using the auxiliary oxygen flowmeters on all the types of anesthesia machines (at the highest scale setting on the flowmeter scale), no anesthesia machine generated sufficient working pressure to drive a jet ventilator. The working pressures varied from 14 to 38 kPa (2–5.5 psi). For instance, the working pressures generated by both types of Draeger anesthesia machine flowmeters at the maximum rated flow (control valve opened to the maximum allowable/calibrated flow) varied between 24 and 28 kPa (3.5–4 psi). These pressures are insufficient working pressures for jet ventilation.

Opening the auxiliary oxygen flowmeter beyond the maximum scale setting had different results for the 2 makes of anesthesia machines:

The working pressures provided by the auxiliary oxygen flowmeter on the Draeger machines were still insufficient to drive a jet ventilator.

The working pressures generated by the Datex-Ohmeda machines at the totally open setting (opened beyond the maximum scale setting) varied between 189 and 248 kPa (27–36 psi), which is adequate for jet ventilation.

The Narkomed 2B and Narkomed 4 anesthesia machines are equipped with auxiliary oxygen flowmeters with the highest rated flow at 10 L/min. The oxygen supply for the Draeger machines' auxiliary oxygen flowmeter passes through the plumbing of the anesthesia machine. The Datex-Ohmeda machines are provided with "external" oxygen flowmeters, which are fed directly from the oxygen pipeline. The auxiliary oxygen flowmeters of the Datex-Ohmeda machines are therefore similar to the wall-mounted oxygen flowmeters in terms of a "direct" oxygen supply and also have the highest oxygen flow rate of 15 L/min on the scale. It is not clear to us whether the different rated flows (10 L/min vs 15 L/min on the auxiliary oxygen flowmeters of the anesthesia machines) are sufficient to explain the differences in working pressures during jet ventilation.

Wall-Mounted Oxygen Flowmeters

At the highest scale setting, none of the wall-mounted oxygen flowmeters provided sufficient working pressure for jet ventilation, as the pressure varied from 24 to 38 kPa (3.5–5 psi), where 103 kPa (15 psi) is considered the minimum working pressure for jet ventilation. At the totally open setting, all wall-mounted oxygen flowmeters provided sufficient working pressure. We considered the lowest measured working pressure of 100 kPa (14.5 psi) of the Puritan flowmeter sufficiently close to 103 kPa (15 psi) to be considered adequate.

Commercially Available Jet Ventilation System

We compared the results from our test setup with a commercially available jet ventilation system. The range of working pressures with a commercially available jet ventilator connected in the conventional fashion directly to a wall oxygen source of 372 kPa (54 psi) varied from 179 to 283 kPa (26–41 psi) (Table 4), which is similar to the results from our test system. Similar to our test system, none of the wall-mounted oxygen flowmeters at the highest scale setting provided sufficient pressure to drive a jet ventilator. Similar to the results from our test system, the totally open setting on the wall-mounted oxygen flowmeters supplied sufficient working pressure, i.e., >103 kPa (15 psi). Similar to our results, the auxiliary oxygen flowmeter on the Draeger anesthesia machine did not provide sufficient pressure. § Given the similarities of results, we therefore conclude that our test device adequately represents a commercially available jet ventilation system.

The strength of the study is that we included all the anesthesia machines and tested several wall-mounted oxygen outlets at different locations, which are in use in a Level I Trauma Center. Bould and Bearfield¹² presented a similar study in 2008 in which the oxygen flowmeter was opened beyond the highest scale setting. Our work expands and amplifies the range of available emergency sources of high oxygen pressure.

A potential weakness of our study is the analog nature of the oil-filled pressure gauge and the possibility that the needle did not have sufficient time to reach the maximum pressure because of possible damping by the oil. However, during early pilot trials, we held the flush button for prolonged periods and no further increase was noted after the first initial rapid (<1 s) increase to the peak pressure. The oil in the pressure gauge also dampened any oscillations, and a stable reading was readily obtained at all stages. The minimum discrimination of the oil-filled pressure gauge is 3.4 kPa (0.5 psi). However, because of the

§This test was performed on the auxiliary flowmeter of a Draeger Narkomed 6400, which is of the same type and construction as those on the Narkomed 4 machines' auxiliary flowmeters described earlier.

large differences between acceptable and not acceptable working pressures, we do not consider this lack of finer discrimination to be important.

CONCLUSION

We conclude that the working pressures from the common gas outlets of the Narkomed 2B and 4 anesthesia machines, the wall-mounted oxygen flowmeters, as well as the auxiliary oxygen flowmeters of the Datex-Ohmeda Modulus and Excel anesthesia machines are sufficient to use for jet ventilation based on criteria from references mentioned earlier.^{3,6}

Wall-mounted oxygen flowmeters do not supply adequate working pressure when the flow is set to the highest scale setting on the flowmeter; jet ventilation requires a greater flow, which is obtained by opening the flowmeters even further (past their "rated" flow). Neither the auxiliary flowmeters of the tested Narkomed anesthesia machines nor the oxygen flush valve of the tested Datex-Ohmeda anesthesia machines will provide sufficient pressures to be used for transtracheal jet ventilation. Because of the variability of a given type of oxygen supply device (e.g., auxiliary oxygen flowmeter), as well as the variability of devices from the same manufacturer, it is important to test each potential high-pressure oxygen source before use to determine whether it actually provides sufficient working pressures during transtracheal jet ventilation.

APPENDIX

Serial numbers of the tested anesthesia machines:

Draeger Narkomed 2B: B-13293, B-14199, B-11035, B-12220, B-14198, B-12218, B-14200, B-12221, B-13294, B-11032, B-11037, B-13289, B-11054, B-11033, B-12219

Draeger Narkomed 4: 10051, 10056, 11547

Datex-Ohmeda Modulus: AMDZ00232, AMFA00259, AMFZ00366

Datex-Ohmeda Excel: AMFZ00367

Serial numbers, respective type numbers of the tested from the wall-mounted oxygen flowmeters:

Timeter ($n = 6$): 10407003, 10660739, 10533276, 10445860, 10407135, 10407155

Precision ($n = 6$): Type numbers IMFA 1001, 5MFA1001, 5MFA1081

Datex-Ohmeda ($n = 6$): AHET31275, AHET31509, AHEX21012, AHET 31242, AHET 31288, AHEX21011

Puritan ($n = 6$): Series B, no serial numbers available

Commercial Jet ventilator (AINCA, Anesthesia Associates, San Marcos, CA):

There are no serial numbers on the devices (Cat. #00-325).

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Closed-Circuit Xenon Delivery Using a Standard Anesthesia Workstation

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BACKGROUND: Xenon (Xe) is an anesthetic with minimal side effects, now also showing promise as a neuroprotectant both *in vitro* and *in vivo*. Although scarce and expensive, Xe is insoluble and patient uptake is low, making closed circuits the optimum delivery method. Although the future of Xe anesthesia is uncertain, effective neuroprotection is highly desirable even if moderately expensive. A factor limiting Xe research in all these fields may be the perceived need to purchase special Xe anesthesia workstations that are expensive and difficult to service. We investigated the practicality of 1) true closed-circuit Xe delivery using an unmodified anesthesia workstation with gas monitoring/delivery attachments restricted to breathing hoses only, 2) a Xe delivery protocol designed to eliminate wastage, and 3) recovering Xe from exhaled gas.

METHODS: Sixteen ASA physical status I/II patients were recruited for surgery of >2 h. Denitrogenation with 100% oxygen was started during induction and tracheal intubation under propofol/remifentanyl anesthesia. This continued after operating room transfer for 30 min. All fresh gases were then temporarily stopped, metabolic oxygen consumption then being replaced with 250-mL Xe boluses until $F_I\text{Xe} = 50\%$. A basal oxygen fresh gas flow was thereafter restored with additional Xe given as required via the expiratory hose to maintain a $F_I\text{Xe} \geq 50\%$. At no time, apart from during circle flushes every 90 min, were the bellows allowed to completely fill and spill gas, ensuring the circle remained closed. On termination of anesthesia, the first 10 exhaled breaths were collected as was residual gas from the circle, allowing measurement of the Xe content of each.

RESULTS: Total Xe consumption, including initial wash-in and circle flushes, was 12.62 (5.31) L or 4.95 (0.82) L/h, mean (SD). However, consumption during maintenance periods was lower: 3 L/h at 1 h and 2 L/h thereafter. Of the total Xe used, 8.98% (5.94%) could be recovered at the end of the procedure.

CONCLUSIONS: We report that closed-circuit Xe delivery can be achieved with a modified standard anesthesia workstation with breathing hose alterations only and that the protocol was very gas efficient, especially during the normally wasteful Xe wash-in. A Xe mixture of $\geq 50\%$ was delivered for up to 341 min (5 h 41 min) and Xe consumption was 4.95 (0.82) L/h, maintenance being achieved with 2–3 L/h. With this degree of efficiency, Xe recovery/recycling at the end of anesthesia may be of little additional benefit.

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Xenon (Xe) is a noble gas with attractive anesthetic properties including minimal side effects and fast onset/emergence.¹⁻⁷ Particularly when combined with cooling, it is also showing promise as a neuroprotectant against hypoxic-ischemic brain injury

based on both *in vitro* and *in vivo* experimental studies by modifying the cellular cascades of damage that occur.⁸⁻¹³ Xe was first approved as an anesthetic in Russia (2002)¹⁴ and has also gained licenses as LENOxe™ (Air Liquide, Paris, France) for anesthesia in Germany (2005), France (2007), and the United Kingdom (January 2009), although use is currently limited to ASA physical status I/II adults. Xe is expensive with considerable regional variation, from US\$60/L for 250-L cylinders (Praxair and Air Liquide Healthcare America Corp.) to \$30/L for 1000-L cylinders for anesthesia-licensed Xe (European Society of Anesthesia meeting 2008, Air Liquide, France, exhibition stand). The high cost could support the belief that Xe would never enter clinical use¹⁵; however, the small blood-gas partition coefficient (0.115)¹⁶ and low patient uptake mean that a closed-circuit delivery method could be cost effective.^{17,18} Closed-circuit breathing systems predate the discovery of anesthesia;

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however, until the 1980s their use was limited because of a lack of gas analyzers. Computerized closed-circuit Xe anesthesia research machines have been produced in the past (PhysioFlex-Xe, Physio, The Netherlands/Dräger, Lübeck, Germany) and at least 1 other machine has recently been commercially released. Even with resources to purchase such a machine, researchers may encounter servicing difficulties if not in the country of manufacture. Although the future of Xe anesthesia remains uncertain, if Xe emerges as an effective neuroprotectant, the moderate cost of closed-circle delivery might still be acceptable. The favorable safety profile could be an additional advantage in such an application.^{19,20}

Regardless of the eventual roles of Xe within medicine, there will be a need for users to limit their consumption independently of their ability to fund gas purchase because global production is relatively fixed while industrial demand is increasing. A low-flow circle might seem to be a reasonable approach; however, if 70% Xe is administered with a total fresh gas flow (FGF) of 500 mL/min (250 mL/min Xe: \$450/h at \$30/L), an adult would take up <20% of this total and >80% would still be lost as waste.²¹ This explains the Russian use of Xe recovery devices with their very low-flow delivery systems. The low patient uptake heavily favors the use of closed circuits for greatest efficiency and responsible use of this gas.

The largest Xe losses from a closed circle occur during periods of high FGF, i.e., during initial Xe wash-in and circle flushes. It has been suggested that Xe recycling might still provide additional efficiency gains.²² The Xe uptake of an adult has been demonstrated clinically to be approximately 2.5 L/h¹⁷ to 3.69 L/h²³ at steady state, usually using modified workstations or dedicated research machines. For example, Luttrop et al. described a "gas piston" to replenish metabolically consumed oxygen and we (JD) have also previously developed a mechanism to perform this task.^{3,17,24,25} In addition, we have also previously built a cryogenic Xe recovery machine.²⁶

In this clinical investigation, however, our aims were to 1) describe and evaluate an arrangement enabling those without access to a specialist Xe workstation to perform closed-circle Xe research, 2) evaluate a delivery protocol designed to minimize Xe wastage, in particular by allowing initial Xe wash-in without Xe loss, and 3) explore, against this efficient delivery regime, whether Xe recycling would be worthwhile.

In addition, we describe an optional optical device to remind the user when it is appropriate to add additional gas to the circle.

METHODS

The conduct of this investigation is summarized in the flow chart of Figure 1.

Equipment

The breathing System

We have previously developed closed-circuit Xe systems with automatic replenishment of metabolic

oxygen consumption, but on this occasion, we deliberately sought to investigate the potential of a mechanically unmodified anesthesia workstation of a general design found in many hospitals. A suitable machine would have manual control of fresh gas delivery (rotameters or similar), a circle with a bag-in-bottle ventilation system that spills excess gas to the scavenging system at end-expiration, and, finally, a residual "safety" oxygen FGF when the oxygen rotameter is turned off that is less than the metabolic oxygen uptake of the patient. In this study, we used an Aestiva/5 machine (Datex-Ohmeda, Helsinki, Finland) with a manufacturer-set residual safety oxygen flow of 50 mL/min. The arrangement of anesthesia machine, low bellows volume sensor, Xe delivery, and monitoring systems is shown in Figure 2.

Gas Analyzers

The breathing system hoses (Flexicare Medical, Mid Glamorgan, UK) were adapted to include Luer lock ports for gas sampling and Xe addition; in addition, an electrochemical cell oxygen analyzer was sited in the inspiratory hose (Teledyne, Viamed, West Yorkshire, UK) with appropriate alarms. A previously described custom-made oxygen/Xe/carbon dioxide analyzer (Bedfont Scientific, Kent, UK) was also used.²⁷

Oxygen and Xe Delivery to Breathing System

Oxygen was delivered via the oxygen rotameter of the anesthetic machine. Xe was delivered by simultaneously pressing 2 buttons on the Xe cylinder regulator, whereupon an electronic solenoid valve would deliver 250 mL of Xe as a group of 5 × 50 mL boluses over 20 s to ensure even mixing of the 250 mL Xe with existing gases in the circle. These were added to the expiratory hose to allow additional mixing in the absorber before gas entered the lungs. These steps were taken to prevent any added Xe directly entering the lungs as an unmixed low-FiO₂ bolus.

Low Bellows Volume Sensor

A standard anesthesia machine can be operated as a closed-circle system by carefully adding fresh gases, so the bellows neither completely fills nor empties. By setting an oxygen FGF closely matching uptake during maintenance, changes in end-expiratory bellows volume develop only very gradually, requiring infrequent correction. Nevertheless, there is perhaps a greater perceived workload for the anesthesiologist. As gas is consumed, the operator must be very vigilant, always ensuring that the bellows never completely empties. We considered the possibility of a "low bellows volume" alert system as a reminder to the operator of the need to introduce additional fresh gases in a timely manner and built an optical device to perform this function (Fig. 3). The design was based on an idea from a previous study and used an infrared beam directed through the bellows housing approximately 10 cm from its base.²⁴ An audible and visible warning was given when the bellows volume decreased to a point at which it no longer

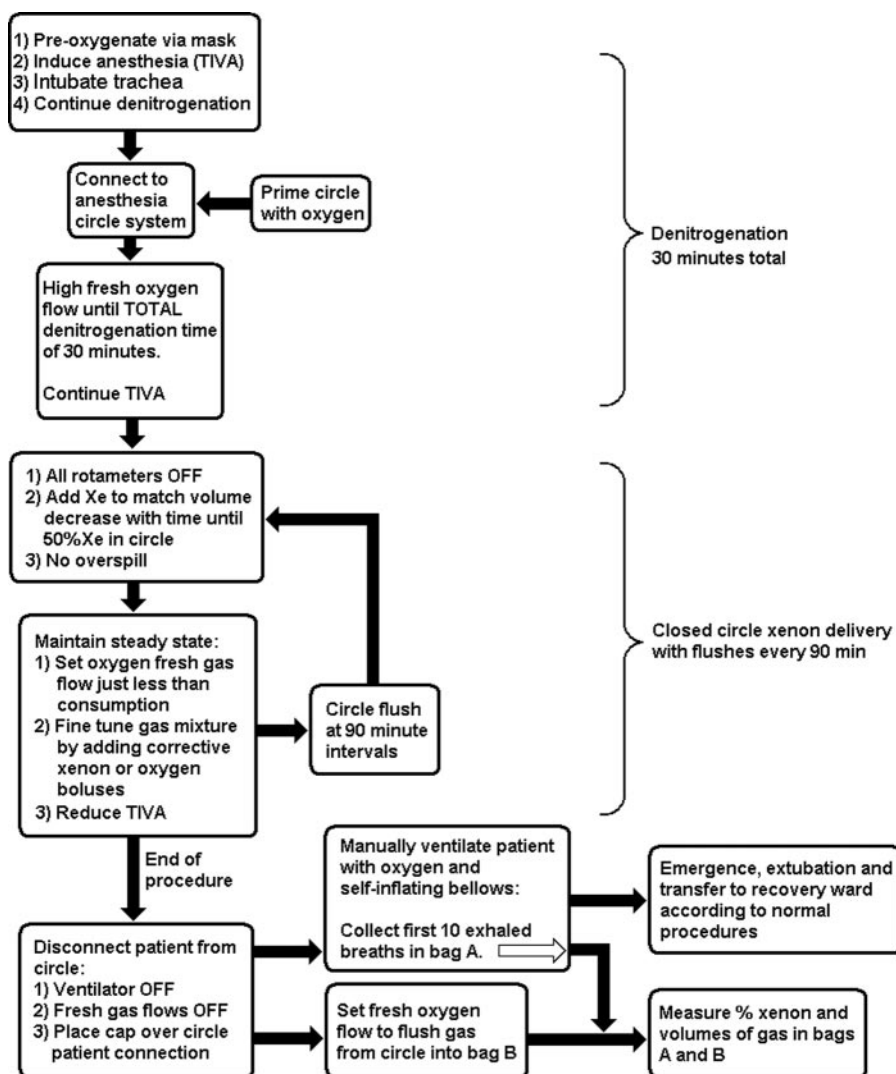


Figure 1. Summary of the experimental protocol.

interrupted the beam at end-inspiration. The infrared emitter and receiver sensor pair were affixed to the outside of the bellows housing, which was not modified in any way, by adhesive tape. The beam was pulsed so the receiver could discriminate between an expected pulse and background interference.

Xe Recycling Machine

This has been built by 1 of the authors and the performance characteristics have been previously described.²⁶

The arrangement of anesthesia machine, low bellows volume sensor, Xe delivery, and monitoring systems is described in Figure 1.

Conduct of Xe Delivery in Patients

This study was approved by the IRB and written informed consent was obtained from each participant. The authors enrolled 16 patients in the study who were ASA physical status I/II having pelvic or complex lower limb orthopedic surgeries lasting longer than 2 h.

Induction of Anesthesia

The patients breathed 100% oxygen via a close-fitting facemask and a non-rebreathing anesthetic circuit at high FGF (>10 L/min) for 5 min to begin the

denitrogenation process. This maneuver prevents nitrogen dissolved in blood/tissues (~1.3 L in a 70 kg male) from emerging via the lungs and diluting the other gases present once the circle is closed.^{28,29} Standard patient monitoring was used. Anesthesia was induced using a propofol target-controlled infusion (TCI) with a target of 4 $\mu\text{g}/\text{mL}$ and remifentanyl 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. A single IV vecuronium dose of 0.1 mg/kg facilitated placement of a cuffed tracheal tube. Denitrogenation continued during the subsequent mechanical ventilation and was completed in the operating room after transfer from the anesthetic room.

Transfer to the Operating Room

On transfer to the operating theater, the patient's lungs were ventilated using an anesthetic machine (Aestiva/5, Datex Ohmeda, Stirling, UK), the circle system of which had been primed with oxygen in advance after a visual leak check (observation of constant bellows height at end-expiration while ventilating a test lung). Denitrogenation continued on 100% oxygen (FGF > 6 L/min) (the circle at this point functioning as a semiclosed system spilling excess gas), until the total denitrogenation period had

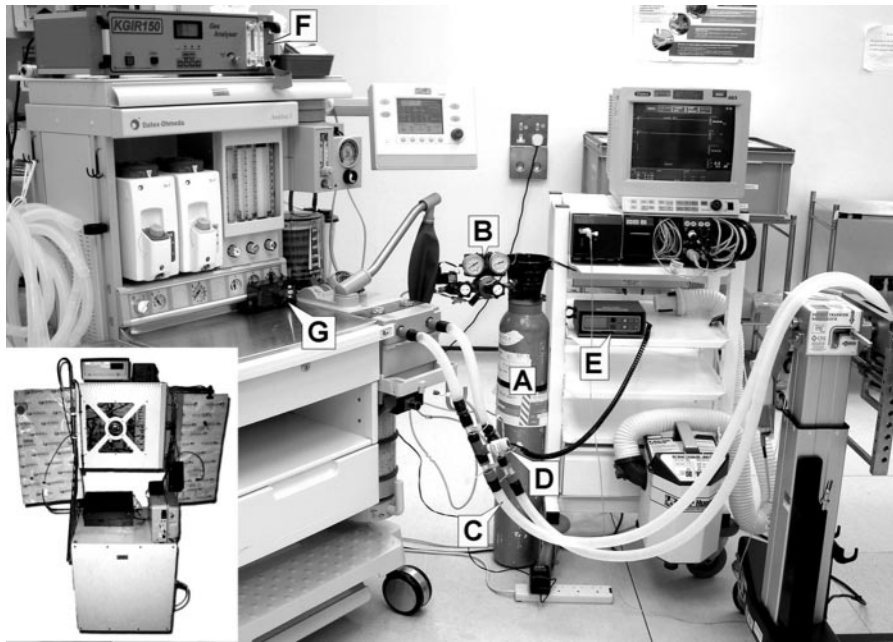


Figure 2. Photograph of equipment assembly (inset: cryogenic xenon [Xe] recovery machine). Xe from the cylinder (A) is delivered in 250-mL aliquots by pressing 2 buttons on the pressure regulator/timed solenoid valve unit (B) to the breathing system hose (C). Gas monitoring is provided by an in-circuit oxygen cell/display (D, E) and a Xe/oxygen/carbon dioxide analyzer (F). The monitor (G) gives a “low bellows volume” warning.

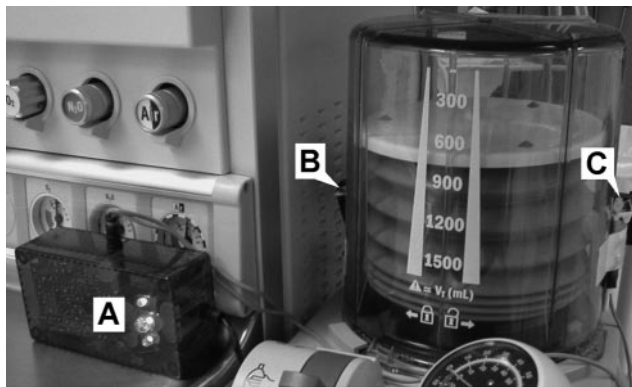


Figure 3. Detail of the “low bellows volume” alert device. Container (A) housed the low-voltage electronics that gave visual and audible warnings if the bellows volume at end-inspiration was low. Two cables terminated in an infrared emitter/receiver sensor pair (B, C), which sent an infrared beam through the bellows housing.

reached 30 min. This duration was based on the experience of Morita et al.³⁰ who demonstrated that rigorous denitrogenation reduces the subsequent need for frequent circle flushing.

Anesthesia during denitrogenation was maintained by propofol/remifentanyl infusions, so this maneuver did not cause surgical delay. Warmed intraoperative fluids were given throughout the surgical procedure as clinically indicated and a patient warming device was used in every case.

Xe Delivery

The objective after denitrogenation was to increase the inspired Xe fraction to $\geq 50\%$ as rapidly as possible without spillage of circle gas, i.e., by not using a high FGF during Xe wash-in and not allowing the bellows to completely fill at end-expiration. We could have conventionally used high FGF wash-in with gas overspill, but this would have proved extremely wasteful

and expensive. Instead, a gradual maneuver was performed during which the metabolic oxygen consumption from the circle was continually replaced by Xe, given as 250-mL (5×50 mL) doses, until a 50% Xe concentration had been reached.

To achieve this, all rotameters were turned off and the circuit was allowed to function fully closed. As the patient metabolically consumed oxygen, the end-expiratory bellows volume decreased at a rate of approximately 200–300 mL/min (minus the residual safety oxygen feed of 50 mL/min remaining after the oxygen rotameter had been turned off). As this volume deficit developed, it was replaced with equivalent volumes of Xe, without allowing the bellows to completely fill and spill excess gas. By adding Xe at a rate matching patient gas uptake, the target Xe concentration of 50% was achieved without Xe loss.

Maintenance of Anesthesia

Once a Xe concentration of $\geq 50\%$ had been attained, the propofol TCI target was reduced according to clinical response. The use of a reduced dose background propofol infusion with Xe follows the practice of other groups because the minimum alveolar anesthetic concentration (MAC) of Xe is 71%, 50% Xe alone (0.7 MAC) would be insufficient for reliable anesthesia. Having reached the target Xe concentration, an oxygen flow equal to the previously observed oxygen uptake of the patient was set (typically 200–300 mL/min). This ensured that the bellows height at end-expiration only changed very slowly with time, requiring infrequent adjustments thereafter. Similarly, during maintenance, the very low Xe uptake rendered the requirement for additional Xe doses less frequent. Guidelines for closed breathing systems recommend flushes at least every 2 h to prevent buildup of trace

gases, such as methane and acetone,^{31,32} and so the circuit was flushed every 90 min.

Circle Flush Procedure

This again was designed to waste as little Xe as possible. Instead of using a high Xe/O₂ FGF maneuver, we set up a 10 L/min fresh gas flow of 100% oxygen for 1 min to displace existing gases from the circle. After this, the procedures previously described for Xe wash-in without overspill and subsequent maintenance were again followed. During this maneuver, the propofol TCI target was temporarily increased.

End of Surgery and Anesthesia

Analgesia was administered before emergence. The oxygen rotameter and mechanical ventilator were turned off. The breathing circuit was disconnected from the patient and capped off at the "Y" piece to retain the contained gas for later collection. The patient was prepared for tracheal extubation while being manually ventilated via the tracheal tube with 100% oxygen via a non-rebreathing bag. The first 10 breaths of exhaled gas generated during this maneuver were collected into a metallic bag (A) for subsequent assay. It was anticipated that these first few exhaled breaths would contain a useful volume of recoverable Xe. The patient was then tracheally extubated and transferred to the recovery ward.

The sealed circle system was flushed with oxygen to propel the contained Xe-rich gas into a second metallic collection bag (B) for analysis. This was done by ventilating a test lung allowing the circle system to "bleed" gas via a Luer lock connector into the empty metallic bag, while simultaneously supplying the circle with fresh oxygen to keep the bellows partially filled.

Additional Procedures

The volume of gas in each collection bag was measured by evacuating their contents using a 210-mL internal volume syringe (Festo DNC-50-100, Esslingen, Germany) and 1-way valve system, whereas the Xe concentration of each was measured using the Xe analyzer. This allowed us to consider whether it would be worthwhile to process this gas using a Xe recovery device.²⁶ No collected Xe was recycled for any subsequent patients in this study.

We used the computer simulation program "Narkup 2000" (D.C. White, Northwick Park Hospital, Middlesex, UK and G. Lockwood, Hammersmith Hospital, London, UK) to estimate tissue Xe uptake over the first 90 min in a 70-kg patient breathing 50% Xe, allowing comparison with our measured values.³³

The data are descriptive with mean (SD) used to describe normally distributed data.

RESULTS

The duration of Xe use was 159 (74) min with a range of 61–341 min.

Xe Delivery

After induction of anesthesia and a 30-min denitrogenation period under total IV anesthesia (TIVA), the subsequent loading period to reach a 50% Xe concentration was 31.7 (17.69) min and required 5.29 (1.02) L of Xe. This improved with practice as the first 8 patients had a load time of 43.1 (18.6) min, whereas in the remaining 8 this reduced to 20.25 (5.06) min.

The circle Xe concentration is shown in Figure 4A. Once 50% Xe had been achieved, the propofol TCI set point was reduced from the initial 4 $\mu\text{g}/\text{mL}$ to 2.42 (0.63) $\mu\text{g}/\text{mL}$ and the Xe concentration during these maintenance phases was 55.08% (3.87%).

The cumulative fresh Xe requirement is shown in Figure 4B. The initial requirement when the circuit volume, functional residual capacity (FRC), and tissues were being loaded with Xe was relatively high, followed by low requirements thereafter. The circle flush maneuvers every 90 min produced subsequent stepwise increases in Xe consumption. The overall Xe consumption with time is alternatively displayed over 30-min time epochs in Table 1.

Because the initial wash-in of Xe took place without any gas overspill, we can compare our observed Xe requirement during the first 90 min before the first circle flush with that mathematically predicted. To bring the Xe concentration of the FRC (approximately 2.8 L in an adult)³⁴ and estimated circuit volume of 4.15 L (datasheet circuit volume 5.5 L minus volume of 2×1.35 kg soda-lime) to 50% would require half this total volume, i.e., 3.48 L of Xe. Added to this would be the predicted patient Xe uptake during the first 90 min, via "Narkup," of 4.17 L giving a calculated total Xe requirement for the initial 90 min of approximately 7.65 L. By comparison, our measured Xe requirement over the first 90 min was 8.29 L. The overall mean Xe consumed per procedure, including wash-in and flushes was 12.62 (5.31) L or 4.95 (0.82) L/h.

For each procedure, we defined each maintenance period as being from the point at which after wash-in, 50% Xe had been reached, or after a flush maneuver, had been restored to 50%. During the first, second, third, and in 1 case fourth of these maintenance periods, Xe was being given at a rate of 3.03 (0.96), 2.10 (0.56), 2.06 (0.88), and 2.21 L/h, respectively. The number of 250-mL Xe boluses given per hour remained consistent between each of the maintenance periods as time progressed, with rates of 13, 9, 9, and 9 per hour during each period, respectively (only 1 patient required a fourth maintenance period).

Xe Recovery

This can be considered in 2 parts: Xe recovered from the circle system and Xe recovered from the patient. The volumes are shown in Table 2.

DISCUSSION

We investigated whether Xe could be administered to patients using a conventional anesthesia machine

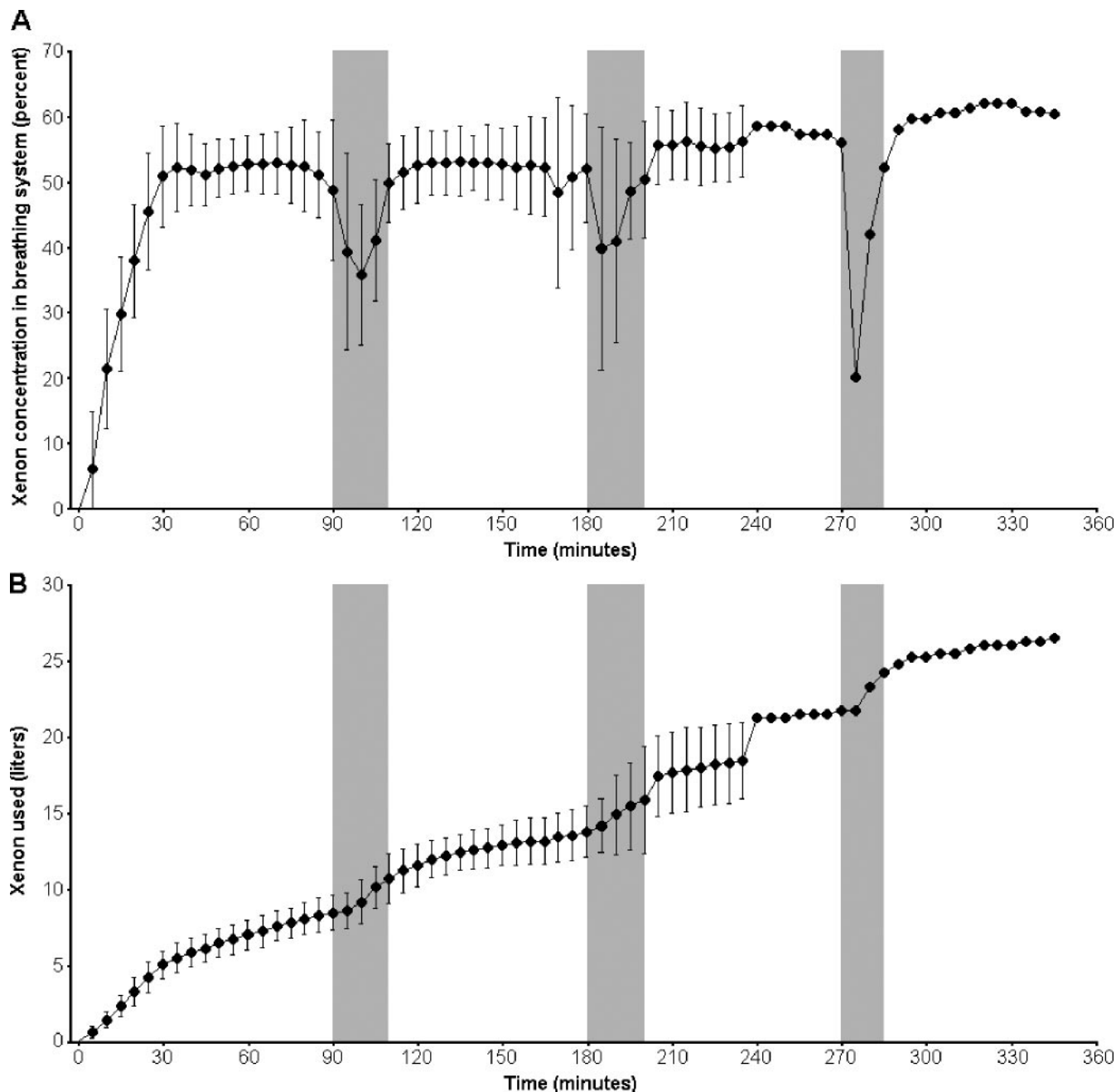


Figure 4. Xenon consumption and concentration in the breathing system. A, Cumulative xenon use with time (pooled data from all patients). Shaded areas represent circuit flushes with fresh gas. B, Xenon concentration in the breathing system (pooled data from all patients). Shaded areas represent circuit flushes with fresh gas.

with modified breathing hoses running as a closed circuit, how efficiently this could be done using a protocol designed to be clinically practical yet absolutely minimize Xe wastage, and finally to investigate whether, having optimized Xe delivery, Xe recovery would then be worthwhile.

Xe has a very low blood/gas solubility ratio of 0.0115,¹⁶ rendering all breathing systems other than closed circuits relatively wasteful. For example, the earliest Russian studies used FGFs of 2 L/min at a cost of US\$ 3600/h (\$30/L), but this method was rapidly abandoned because it was too expensive.³⁵

The overall Xe consumption observed in this study was 4.95 (0.82) L/h (\$148.5/h at \$30/L), whereas

steady-state maintenance required approximately 2–3 L/h (\$60–90/h at \$30/L).

The use of TIVA permitted a gradual Xe wash-in maneuver while avoiding gas loss, provided anesthesia without surgical delay during denitrogenation, and provided anesthesia during subsequent circle flush maneuvers, which again avoided a high Xe FGF. Our Xe requirements during the first 90 min were close to the values estimated from circle + FRC volumes and mathematically predicted patient uptake.

Xe is extracted from air as a byproduct of industrial oxygen production, so global production is relatively fixed at 9–12 million L/yr. Industrial demand has greatly increased the price over the last 10 yr from the

Table 1. Xenon (Xe) Requirements for Each 30-min Period

| Time interval | n | Volume Xe used (L) | Xe requirement during maintenance period only (from F _i Xe 50% until next circle flush or end of case) (L) |
|---------------|----|--------------------------|---|
| 0–30 | 16 | 5.05 (0.90) ^a | 3.03 (0.96) |
| 30–60 | 16 | 1.95 (0.73) ^a | |
| 60–90 | 13 | 1.29 (0.64) | |
| 90–120 | 11 | 2.88 (0.99) ^b | 2.10 (0.56) |
| 120–150 | 9 | 1.03 (0.36) | |
| 150–180 | 6 | 1.07 (0.76) | |
| 180–210 | 3 | 2.67 (1.23) ^b | 2.06 (0.88) |
| 210–240 | 3 | 0.75 | |
| 240–270 | 1 | 0.5 | |
| 270–300 | 1 | 3.5 ^b | 2.21 |
| 300–330 | 1 | 0.75 | |
| 330–345 | 1 | 0.5 | |

Data are mean (sd).

^a Includes xenon used during wash-in into the combined volume of the functional residual capacity and circle.

^b Includes xenon volume used during a circle flush maneuver.

often-quoted value of \$10/L. If, hypothetically, 1 million liters of Xe per year could be set aside for medical use, then, even if Xe consumption could be optimized to perhaps 15 L per patient, this would still only provide approximately 67,000 adult interventions globally per annum.

In 1999, based on the observations of Goto et al.,⁶ Nakata et al.²⁹ performed a cost analysis of closed-circuit 1 MAC (71%) Xe administration assuming a perfect closed circle. For a 240-min procedure, the predicted maintenance Xe consumption was 2.9 L/h, whereas the high FGF Xe wash-in and hourly circle flushes would have consumed a further 6.9 L and 20 L, respectively. Against these optimum values, our overall Xe consumption of 2.06–3.03 L/h during maintenance and 4.95 (0.82) L/h overall appear competitive, suggesting that our protocol for optimal cost containment was effective. Contemporary published cost comparisons of volatile anesthetics for long procedures gave values of \$13/h (closed-circuit N₂O/isoflurane),²⁹ \$23.5/h (semiclosed N₂O/isoflurane),²⁹ \$5.7/h (closed-circuit N₂O/sevoflurane),³⁶ and \$21/h (semiclosed N₂O/sevoflurane).²⁹ Propofol infusion techniques at that time were twice the cost of volatile anesthetics (FGF 1.5–2 L/min).³⁷ They concluded that, at a price of approximately \$10/L, maintenance of

closed-circle Xe anesthesia (\$20–\$30/h) remained comparable with other forms of anesthesia, recommending efforts be directed to further reduction of Xe wash-in and flush costs, which we have now demonstrated are possible. At the current increased price of \$30/L or even \$60/L in some countries, these considerations become even more important.

Although the future of even closed-circle Xe anesthesia remains uncertain, if Xe does find a role as a neuroprotectant because of the limited alternatives, the moderate costs may be acceptable.

Recycling of collected Xe from gas collected during emergence and from the circle would have recovered, with no processing losses, 8.98% of the total Xe used. This fraction could have been increased by collection of waste gas during the flush maneuvers. We administered 10 breaths of approximately 600 mL volume to each of these predominantly large male patients to recover Xe from the lungs. Allowing for anatomical dead space, this limited alveolar ventilation would not have optimally washed out Xe from the FRC and could be improved. Similarly, a more efficient way to recover Xe from the circle at the end of the case would have been to temporarily “unfold” the circle to functionally form a tube, flushing its contents into a collection bag by adding oxygen at the opposite end (the reverse of a priming technique proposed by Saito et al.).³⁸ Although with very low-flow systems (Russian experience), Xe recycling has been found to be necessary,¹⁴ we suggest that with a closed-circle regime optimized to minimize Xe wastage, recycling may not be worthwhile especially if the costs of consumables, servicing, and recertification as a medical gas are also considered.

To avoid Xe spillage during Xe wash-in, the initial Xe delivery rate had to exactly replace the emerging volume deficit. The rate of development of this deficit was, ignoring Xe uptake, equal to the metabolic oxygen consumption minus the “safety” residual oxygen flow from the oxygen rotameter when in the “off” position. The closer this residual safety oxygen flow is to the metabolic consumption, the slower the maximum possible addition rate of Xe (without overspill) becomes.

Table 2. Overview of Xenon-Containing Gas Mixtures Collected at the End of Each Procedure and Reductions in Total Xenon Use Per Procedure Achievable by Waste Gas Reprocessing

| | Gas recovered from first 10 exhaled breaths at end of procedure | Gas recovered from breathing system at end of procedure |
|--|---|---|
| Volume of collected gas (L) | 6.13 (1.99) | 3.20 (1.77) |
| Xenon fraction in collected gas (%) | 9.3 (2.55) | 12.49 (5.22) |
| Volume of xenon within this collected gas (L) | 0.55 (0.18) | 0.41 (0.29) |
| Fraction of total xenon volume used per procedure recoverable from each portion of collected gas (%) | 4.95 (2.95) | 4.03 (3.7) |
| Recoverable percentage of the total delivered xenon volume | 8.98 (5.94) | |

Data are mean (sd).

An alternative maneuver to accelerate wash-in without Xe loss would have been to prime the circle with an oxygen/Xe mixture.³³ We chose to prime the circle with oxygen because it allowed us to complete denitrogenation in the operating room under TIVA without surgical delay after induction in an adjacent room, which is traditional UK practice. It would, however, be equally possible to perform the entire procedure in the operating room.

Our Xe wash-in times shortened as our technique improved. Originally, as closed-circuit Xe delivery commenced after high-flow oxygen denitrogenation, the bellows of the oxygen-containing circle would be almost full, and Xe would then be gradually added to replace the volume deficit produced by metabolic oxygen consumption. We realized that it would be more advantageous for the bellows position to be partially empty at this time, creating an immediate additional spare capacity in the circle of up to 1 L into which fresh Xe could be added to allow more rapid attainment of the target circle Xe concentration while still avoiding gas spillage.

Apart from a means of adding Xe to the expiratory hose, the only other essential equipment requirement of this arrangement is a means of monitoring the circle gas composition. Oxygen analyzers are readily available. Xe measurement systems have to be specially commissioned; however, they do use readily available industrial components. These usually exploit the high density of Xe relative to other gases to allow measurement via the thermal conductivity of the gas sample (katharometry) or the speed of sound within it.²⁷ The only commercially available Xe/O₂ monitor the authors have experience with is the GKM-03-INSOVT mainstream Xe anesthesia analyzer from St. Petersburg, Russia (obtainable via Alfa-Impex Oy, Helsinki, Finland), which has standard Western taper fittings. In summary, a minimum hypothetical "kit" of parts to use for this technique would comprise, in addition to a standard anesthetic machine of the general design previously outlined, modified breathing hoses for monitoring/gas delivery, a means of adding small volumes of Xe to the expiratory hose, and a means of Xe/oxygen monitoring.

The repeatability of the volumes produced by our electronic Xe dosing system aided our Xe consumption calculations; however, such a device is not essential and a calibrated Xe rotameter would suffice if used with care.

We have shown that, with care, efficient closed-circuit Xe delivery can be achieved using a substantially conventional anesthetic machine and a protocol designed primarily to minimize Xe wastage. The low bellows warning device was a useful aid and, although not essential, provided a timely reminder to the user to either increase the oxygen rotameter flow during maintenance or add Xe. With any conventional

anesthesia machine running fully closed, the anesthesiologist must ensure meticulous monitoring of the circle volume and gas content.

With fresh breathing system filters after each anesthetic, subsequent cases could advantageously reuse the circuit volume, now primed with Xe as a means of achieving further reductions in overall Xe use.

In conclusion, for a 50% Xe administration period of up to 341 min, using an anesthetic machine in this manner, the overall Xe consumption can be as low as 4.95 (0.82) L/h and maintenance is possible with approximately 2–3 L/h—close to the theoretical minimum. This efficiency of gas delivery was such that a Xe recovery system might not be worthwhile. Such a regime might facilitate more widespread clinical Xe research by removing the purchasing cost and servicing difficulties of a dedicated Xe workstation and by minimizing consumable Xe costs.

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Dental Sedation by Dentists: A View From Anesthesiologists Working in Central Western Brazil

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BACKGROUND: Anesthesia care has been provided by diverse health professionals worldwide, but little is known about anesthesiologists' views about this. Using a survey, we sought the opinions of a group of Brazilian anesthesiologists regarding nitrous oxide/oxygen and oral minimal/moderate sedation performed by dentists.

METHODS: A 3-part postal questionnaire was sent to 206 physician anesthesiologists working in the state of Goiás, in Central Western Brazil. Part 1 consisted of 4 questions describing respondents' characteristics: gender, time elapsed since completion of the residency program, and experience in providing sedation and general anesthesia for dental treatment. In Part 2, respondents were asked to give their opinions on 11 statements about sedation performed by dentists. Possible responses ranged from total disagreement to total agreement (minimum score = 11 and maximum score = 55). Part 3 was a section for general comments. Data were analyzed by k-means clusters, χ^2 , and Student's *t*-test.

RESULTS: The response rate was 53.8% (111 questionnaires). Most anesthesiologists (85.6%) had rarely or never provided sedation or general anesthesia for dental treatment, and 92.8% disagreed with the statement that dentists can administer moderate sedation in the dental office. Two clusters representing more favorable ($n = 21$) or less favorable ($n = 90$) opinions were established. Anesthesiologists in the "less favorable" group had more experience with dental sedation ($P = 0.006$) and dental general anesthesia ($P = 0.008$) than those in the "more favorable" group. Gender and time elapsed since residency completion did not significantly affect anesthesiologists' opinions.

CONCLUSIONS: Many anesthesiologists in Central Western Brazil do not sedate dental patients and are not confident that dentists are able to do it. Dental sedation is an issue that still needs to be clarified in this region; the respective roles of physicians and dentists need to be determined to benefit the population.

(Anesth Analg 2010;110:110-4)

Minimal and moderate sedation in dental offices can be performed by practitioners who are not specialists in anesthesiology as long as guidelines for minimizing risks to patients are followed.¹ However, departments of anesthesiology are responsible for providing procedural sedation,² including procedural sedation in dentistry.³ The role of the anesthesiologist in the dental office sedation process includes personally administering anesthesia, training and supervising nonanesthesiologist providers, looking after the care environment, and promoting the quality and safety of care.²

Procedural sedation delivery varies around the world. There are regions where anesthesiologists are the sole providers of such care in surgery units (e.g., most of Europe), others where a few trained nonanesthesiologists provide sedation in specified circumstances and locations (e.g., the United Kingdom [UK]), and other countries where multiple nonphysician professionals provide sedation in diverse settings (e.g., United States and Canada).⁴ In Brazil, anesthesiology is a specialty restricted to physicians. After a 6-yr medical undergraduate course, physicians can apply for a 3-yr anesthesiology residency program. Brazilian law also allows qualified dentists to perform analgesia/sedation and hypnosis.

Practitioner skills and practice standards are the general areas of controversy in procedural sedation.^{4,5} According to the Joint Commission on Accreditation of Healthcare Organizations, a qualified hospital sedation provider is one who has "at a minimum had competency-based education, training, and experience" in evaluating patients, performing moderate sedation, and rescuing patients who slip into a deeper-than-desired level of sedation.⁶ It has been claimed that a shortage of anesthesiologists is one factor that has limited the expansion of sedation services.^{2,5,7}

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There is a wide range of dental training experiences to prepare the dentist to provide dental sedation.⁸ With an increasing demand for sedation in dentistry,³ it is necessary to clarify professional roles in providing this kind of sedation.

Information about anesthesiologists' perceptions on the provision of dental sedation is lacking, although we found one report on this topic.³ This survey sought the opinions of a group of Brazilian anesthesiologists regarding nitrous oxide/oxygen and oral minimal/moderate sedation performed by dentists. This information may help researchers and clinicians in the development of strategies to improve patient dental care.

METHODS

Sample

This study was approved by the IRB of the Federal University of Goiás. The sample consisted of 206 physicians registered as anesthesiologists in the state of Goiás, Central Western Brazil, in the second half of 2006. Although there were 342 registered anesthesiologists in Goiás, no contact information for 136 of them was available to the research team. Written informed consent was obtained from all subjects, and their anonymity was protected.

Questionnaire

The questionnaire used in this study was developed in 2 phases. The first phase consisted of a qualitative study: one researcher (WJV) conducted in-depth interviews with a convenience sample of 10 anesthesiologists using a 4-question guide focusing on their perceptions about sedation or general anesthesia for dental treatment, sedation administered by dentists, and their experience with dental sedation. The interviews were audiotaped, and the responses were transcribed; an interpretative analysis led us to the respondents' most commonly held ideas: sedation in the dental office is valid for adults but not indicated for children; dental sedation should preferably be performed in a hospital; chloral hydrate is no longer used by anesthesiologists to sedate children; midazolam is the premedication of choice; dentists could administer dental sedation if they were able to rescue a patient from emergency situations; and general anesthesia in the hospital setting is highly indicated for some cases, for example, special needs patients or those who will undergo painful dental procedures. These ideas were the basis of the questionnaire that was tested in the pilot study.

For the phase 2 (pilot) study, 10 residents in anesthesiology were invited to complete the questionnaire. After data analysis and minor changes, the final version was administered to all the anesthesiologists who did not take part in the preliminary phases of this study.

The final version of the questionnaire consisted of 3 parts. Part 1 included 4 questions to elicit demographic data: gender, length of time (years) since completing the residency program, and frequency of dental sedation and dental general anesthesia by the anesthesiologists (never, less than once a month, or more than once a month). Part 2 (first column, Table 1) sought their opinions about dentist-performed sedation through 11 statements, each with 5 possible Likert scale responses: strongly disagree (Score 1), disagree (Score 2), unsure (Score 3), agree (Score 4), and strongly agree (Score 5). Statements 2, 3, and 10 had reversed scores for inferential analysis. The minimum and maximum possible scores were 11 and 55, respectively; the higher the score, the more positive were the opinions about sedation performed by dentists. There was also a section for voluntary general comments (Part 3).

Data Collection

This study was designed as a cross-sectional postal questionnaire-based survey. An envelope containing a cover letter, the informed consent form, the questionnaire, and a stamped return envelope was mailed to 206 registered anesthesiologists working in the state of Goiás. One month after the first attempt, another envelope was sent to those individuals who did not answer the first time. Those who did not return the questionnaire after 2 attempts were excluded from the study.

Statistical Analysis

Cronbach's α was used to investigate the internal consistency of the questionnaire, and its initial value for the 11 questions was 0.64. Then, we sequentially removed 1 question at a time until we obtained the best possible solution (Cronbach's α 0.80) with 4 remaining items: question numbers 1, 4, 6, and 9.

Because there was no dependent variable, a k-means cluster analysis was performed to divide the answers to Part 2 of the questionnaire into 2 clusters where scores from 1 cluster were more similar to each other than scores from the other cluster. The k-means algorithm is a partition method that uses an iterative refinement technique. It assigns each point to the cluster whose center (centroid) is nearest using Euclidean distance. The center is the average of all the points in the cluster, that is, its coordinates are the arithmetic mean for each dimension separately over all the points in the cluster. The iteration continues until the number of objects changing clusters is below a user-specified threshold. The algorithm seeks to minimize within-cluster variance and maximize variability between clusters in an analysis of variance-like fashion.⁹

The clusters were named "more favorable" and "less favorable" opinions toward dental sedation practiced by dentists, and they were compared by Student's *t*-test. χ^2 tests and Student's *t*-test were used to compare the 2 clusters in regard to the independent

Table 1. Score Frequency from the Anesthesiologists' Answers

| Statements | Scores, <i>n</i> (%) | | | | |
|---|-----------------------|--------------|------------|------------|--------------------|
| | Strongly disagree (1) | Disagree (2) | Unsure (3) | Agree (4) | Strongly agree (5) |
| 1. Dentists are able to provide moderate sedation in the dental office | 91 (82.0%) | 12 (10.8%) | 8 (7.2%) | 0 | 0 |
| 2. In the dental office, moderate sedation should be provided by medical anesthesiologists (<i>r</i>) ^a | 0 | 18 (16.2%) | 5 (4.5%) | 40 (36.0%) | 48 (43.2%) |
| 3. Moderate sedation should be provided in a hospital setting (<i>r</i>) ^a | 0 | 8 (7.2%) | 12 (10.8%) | 61 (54.9%) | 30 (27.0%) |
| 4. Dentists are able to provide oral sedation | 53 (47.7%) | 37 (33.3%) | 10 (9.0%) | 11 (9.9%) | 0 |
| 5. Dentists are able to provide basic life support in an emergency situation | 52 (46.8%) | 27 (24.3%) | 12 (10.8%) | 20 (18.0%) | 0 |
| 6. Oral sedation is a safe procedure for other practices such as radiological clinics | 35 (31.5%) | 35 (31.5%) | 22 (19.8%) | 19 (17.1%) | 0 |
| 7. A 96-h program ^b is sufficient to enable a dentist to provide inhalational sedation with nitrous oxide and oxygen at his or her office | 74 (66.7%) | 30 (27.0%) | 7 (6.3%) | 0 | 0 |
| 8. A dentist can provide oral chloral hydrate sedation for ASA PS 1 children | 59 (53.2%) | 29 (26.1%) | 14 (12.6%) | 9 (8.1%) | 0 |
| 9. A dentist can provide oral midazolam sedation for ASA PS 1 children | 78 (70.3%) | 26 (23.4%) | 6 (5.4%) | 1 (0.9%) | 0 |
| 10. General anesthesia is the first choice for dental treatment of patients that do not cooperate with nonpharmacological behavior management methods (<i>r</i>) ^a | 12 (10.8%) | 45 (40.5%) | 12 (10.8%) | 31 (27.9%) | 11 (9.9%) |
| 11. If dentists were trained to provide moderate sedation in the dental office there would be less referral for dental treatment under general anesthesia | 27 (24.3%) | 39 (35.1%) | 20 (18.0%) | 10 (9.0%) | 15 (13.5%) |

^a Scores were reversed (*r*) for 5 to 1.

^b Bylaw of the Brazilian Dental Association.

variables (Part 1); the frequency of anesthesiologists' experience in providing dental sedation or dental general anesthesia was dichotomized as "yes" (regularly provided) or "no" (never or rarely provided). Statistical analyses were performed using SPSS for Windows, version 10.0 (SPSS, Chicago, IL).

RESULTS

One hundred eleven anesthesiologists answered Parts 1 and 2 of the questionnaire completely (response rate 53.8%). They were mostly men (85.6%) and had been practicing in this specialty for 1–34 yr (mean 12 yr). The majority of anesthesiologists had never (54.1%) or rarely (31.5%) (i.e., less than once a month) provided dental sedation in a dental office. General anesthesia for dental treatment was routinely (more than once a month) practiced by only 5.4% of anesthesiologists in this sample.

Low scores were observed in the second part of the questionnaire (11–32 of a maximum of 55, mean 21.4, and *SD* 4.9), pointing to the anesthesiologists' resistance to having dentists provide sedation (Table 1). Most of them disagreed with the statements that dentists can provide moderate sedation (92.8%), are able to manage an emergency situation (71.1%), or are adequately prepared by a 96-h program to provide nitrous oxide/oxygen sedation (93.7%). Instead, most

anesthesiologists (79.2%) thought that moderate sedation should only be administered by anesthesiologists in a hospital setting (81.9%).

Only questions 1, 4, 6, and 9 were considered for bivariate analysis because together they provided the best internal consistency for the scale. A cluster analysis was performed to divide the differences of opinion into 2 clusters. The first cluster included the anesthesiologists whose opinions about moderate sedation provided by dentists were more favorable (*n* = 21), with total scores ranging from 20 to 32. The second cluster included anesthesiologists who had less favorable opinions (*n* = 90, total scores ranging from 11 to 27). There were significant differences in anesthesiologists' opinions between the clusters regarding the 4 questions (Table 2). Differences between clusters were statistically significant in regard to 2 independent variables: there were more anesthesiologists who had provided dental sedation and/or general anesthesia in the cluster of less favorable opinions (Table 3).

Part 3 of the questionnaire, which focused on the inability of the dentist to handle adverse events related to sedation (*n* = 7), anesthesiology as a role of the specialized physician (*n* = 7), or both (*n* = 1), was completed by 13.5% of respondents. Some typical comments were:

Table 2. The Most Relevant Questions About the Opinions of Anesthesiologists About Dental Sedation Provided by Dentists

| Statements | Mean scores (sd) | | P* |
|--|----------------------------------|----------------------------------|--------|
| | More favorable opinions (n = 21) | Less favorable opinions (n = 90) | |
| Dentists are able to provide moderate sedation in the dental office | 2.29 (0.64) | 1.01 (0.10) | <0.001 |
| Dentists are able to provide oral sedation | 2.71 (1.01) | 1.60 (0.83) | <0.001 |
| Oral sedation is a safe procedure for other practices such as radiological clinics | 3.86 (0.36) | 1.84 (0.79) | <0.001 |
| A dentist can provide oral midazolam sedation for ASA PS 1 children | 2.24 (0.77) | 1.17 (0.36) | <0.001 |
| Total scores | 28.10 (3.40) | 19.83 (3.67) | <0.001 |

* Student's *t*-test.

Table 3. Associations Between Anesthesiologists' Opinions About Dental Sedation Provided by Dentists and Independent Variables

| Independent variables | More favorable opinions (n = 21) | Less favorable opinions (n = 90) | P* |
|---|----------------------------------|----------------------------------|-------|
| Gender, n (%) | | | |
| Female | 2 (12.5%) | 14 (87.5%) | 0.732 |
| Male | 19 (20.0%) | 76 (80.0%) | |
| Time elapsed (yr) after residency completion, mean (sd) | 14.33 (8.94) | 11.50 (6.89) | 0.113 |
| Have provided dental sedation, n (%) | 4 (7.8%) | 47 (92.2%) | 0.006 |
| Have provided dental general anesthesia, n (%) | 2 (5.3%) | 36 (94.7%) | 0.008 |

* Fisher's exact test, Pearson χ^2 , and Student's *t*-test.

"It is extremely risky to have other professionals such as dentists provide any kind of sedation because they do not have the formal education to do this. Every human body is different. We never know a particular body's response to a particular sedative. That is why an anesthesiologist attends a residency program for so many years: to be prepared for an unwanted response from the patient. We cannot agree to sedation being left in incompetent hands." (A97)

"Only anesthesiologists are able to manage all topics related to procedural sedation. Dentists must not meddle in professional business for which they are not competent." (A22)

DISCUSSION

This group of Brazilian anesthesiologists held unfavorable views about dentists providing sedation, especially those physicians who had already conducted dental sedation and/or dental general anesthesia. Although this was not a national survey, it highlighted some findings that deserve further consideration.

The anesthesiologists did not approve of dentists administering moderate sedation, and one of the reasons for this was that they were not confident that dentists are competent to provide sedation. However, many anesthesiologists in other studies realize that it is unrealistic to expect anesthesiologists to provide all sedation for dental treatment, and that dentists should be trained to use sedation techniques.³ In our study, a few anesthesiologists agreed that 96 h of training (as legally required by the Brazilian Dental Association) was satisfactory to educate dentists to provide inhaled sedation with nitrous oxide and oxygen. However, the American Dental Association has determined that this type of course should last a minimum of 14 h, including a clinical component during which competency in inhaled sedation technique is achieved, and that it can be completed as a part of a predoctoral dental education program or as a postdoctoral continuing education competency course.¹⁰ Furthermore, Scottish anesthesiologists approved the use of this kind of inhaled sedation by dentists in hospitals (81%) and dental offices (72%).³

Many dentists think that they should receive formal education in sedation.^{8,11,12} General dental practitioners have low overall satisfaction with the quality of sedation education in US dental schools,¹² whereas 49% (*n* = 227), 47% (*n* = 216), and 58% (*n* = 265) of UK dentists find their training in oral sedation, inhaled sedation, and IV sedation, respectively, less than adequate.⁸ From another perspective, undergraduate students attending dental school in the UK and Ireland were reported to be receiving more didactic teaching about, and hands-on training in, inhaled and IV sedation.¹³

There are two other important factors supporting the need to teach dentists to provide dental sedation. The first is an increase in awareness by the population and the wish to have sedation to alleviate their anxiety during dental procedures.^{12,14,15} There is often heavy demand for pediatric sedation in many different settings including dentistry in a hospital setting and outside the operating room.¹⁶ The second factor is the desire of dentists to deliver this kind of service.^{12,17} Of 237 dentists in Canada, for example, 80% believe that nitrous oxide and oxygen sedation should be included among the treatments that a licensed practitioner can provide, and 50% believe that IV sedation should be included.¹⁸

Approximately 22% of the 111 anesthesiologists in the present survey agreed that the provision of moderate sedation by the dentist would reduce referrals

for general anesthesia, and this expectation was investigated and confirmed in a study about midazolam sedation for dental treatment of children.¹⁹ Many anesthesiologists were opposed to the dentist having a role in sedation. To avoid a continuing battle, health professionals and institutions could develop or endorse minimum training requirement guidelines for dentists wishing to practice sedation.³ Anesthesiologists could help professionals and patients by sharing their knowledge with and providing their guidance and oversight to others who might provide hands-on care.² Also, it should be emphasized that adverse events occur in pediatric sedation regardless of physician type (including dentists), but complications are related to the skill set of the practitioner.²⁰

Although anesthesiologists were not as favorable to dentists providing sedation, we attempted to create 2 groups that would represent more or less favorable opinions, and cluster analysis proved that this split was valid. Perhaps if we had had more groups, the results of the statistical associations would have been different. In fact, a shortcoming of this study is that its sample size was restricted to one Brazilian state, but our response rate might be acceptable for this type of survey. In fact, factors influencing response rates in this study might include unwillingness to participate or lack of interest in the subject. However, we expect to stimulate other research groups to study this topic in different regions.

Furthermore, because most of the anesthesiologists did not regularly provide dental sedation or general anesthesia, we could hypothesize that their responses might be affected by factors not measured by the instrument, such as severity in assessment of this subject or even halo error.²¹ Such sources of rater biases must be considered when interpreting or generalizing our results.

Interestingly, anesthesiologists who had provided dental sedation and/or general anesthesia were less permissive of dentists performing this procedure. However, we were not able to explain whether this group was more concerned about sedation-related risks, more aware of the dentists' limitations, or more concerned with the financial implications of having appropriately trained dentists performing sedation/IV analgesia in the dental office. Moreover, because dental general anesthesia has been conducted in a hospital setting in Brazil, these anesthesiologists may have considered dental general anesthesia an efficient solution for healthy patients who need dental anxiety control, despite waiting lists for operating rooms, nosocomial infection, and financial costs.²²

Most of the anesthesiologists surveyed disagreed with sedation provided by dentists in the dental

setting. Instead, they were favorable to hospital-based dental moderate sedation or general anesthesia that they themselves performed. However, very few of these anesthesiologists provide such care.

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The GlideScope Facilitates Nasogastric Tube Insertion: A Randomized Clinical Trial

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BACKGROUND: The GlideScope (Saturn Biomedical Systems, B.C., Canada) is a reusable videolaryngoscope and is considered an effective device for tracheal intubation. We designed this study to evaluate the application of this device in nasogastric tube (NGT) insertion.

METHODS: This randomized clinical trial was performed at a teaching hospital on 80 adult patients who required intraoperative placement of an NGT. The patients were divided into 2 groups (the control and the GlideScope group) using computerized, random allocation software. In the control group, the NGT was inserted blindly as commonly performed in operating rooms; however, in the GlideScope group, the tube was inserted with the assistance of a GlideScope. The number of attempts for NGT insertion and the time required for inserting the NGT properly along with the occurrence of possible complications were recorded.

RESULTS: The mean intubation time in the GlideScope group was 27.7 ± 20.7 s shorter than that in the control group. NGT insertion in the first attempt was successful in approximately 85% of the patients in the GlideScope group; in the control group, however, the tubes were inserted successfully after the first attempt in 57.5% of the patients. Complications were reported in 14 patients (35%) of the control group and 8 patients (20%) of the GlideScope group.

CONCLUSION: GlideScope facilitates NGT insertion and reduces the duration of the procedure.

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The insertion of a nasogastric tube (NGT) in anesthetized, paralyzed, and tracheally intubated patients can be challenging for even the most experienced anesthesiologist.¹

Various techniques have been attempted to facilitate NGT insertion, but none of them has been reported to be universally successful. Some have suggested that deflating the endotracheal cuff will decrease the esophageal compression, and therefore facilitate the insertion of the NGT.² Kayo et al.³ showed that using a 5-cm-height pillow can facilitate NGT insertion in anesthetized patients. Hung and Lee⁴ used a water-fill method to facilitate NGT insertion. Forward displacement of the larynx,⁵ the use of split endotracheal tubes placed via the nasoesophageal route,⁶ the use of the nasopharyngeal airway to serve as an obturator,⁷ the immersion of the NGT in ice-cold water to stiffen the NGT,⁸ the forward neck flexion,⁹ and insufflations of air in the oropharynx

to open the upper esophageal sphincter¹⁰ are among the methods proposed to aid the NGT insertion process.

In addition to these maneuvers, visualization-aided modalities have also been introduced to facilitate NGT insertion.^{1,11,12} Few reports have assessed the role of the GlideScope (Saturn Biomedical Systems, B.C., Canada), an effective device used in tracheal intubation, in facilitating NGT insertion^{2,13}; therefore, this study was designed to evaluate the effectiveness of this device as an aid to NGT placement.

METHODS

After receiving Tehran University of Medical Sciences Ethics Board approval, this prospective, randomized, clinical trial was performed in the operating room of a teaching hospital affiliated with Tehran University of Medical Sciences. Written informed consent was obtained from all patients before entering the operating room.

Eighty adult patients who required NGTs during operations on the gastrointestinal tract, gall bladder, and/or biliary tract were enrolled in the study. Patients who had the criteria for difficult intubation (Cormack and Lehane and/or Mallampati scores of 3 or 4), along with patients with significant deformities of the chin, pharynx, and/or larynx; those having abnormal airway anatomy, base of skull lesions, upper

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airway tumors, hemorrhagic disorders (abnormal prothrombin time, partial thromboplastin time, and platelet disorders), and esophageal stenosis; and/or those with a recent history of esophageal anastomosis, or history of head and neck radiotherapy, were excluded from the study.

Before induction of anesthesia, the patients' nares were checked for possible obstructions; this was assessed by having the patient sniff while the opposite nostril was occluded. The patients were premedicated with midazolam (0.03 mg/kg), fentanyl (2 $\mu\text{g}/\text{kg}$), and lidocaine (1 mg/kg). Propofol (1.5 mg/kg) and atracurium (0.5 mg/kg) were used for induction of anesthesia. A Macintosh laryngoscope was used for tracheal intubation in all patients. Anesthesia maintenance was accomplished with continuous infusion of propofol (100–300 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and alfentanil (0.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) through an infusion pump (Model OT-601, JMS, Hiroshima, Japan). Atracurium (0.5 mg $\cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was infused using a syringe pump (Model SP-100 s, JMS) for intraoperative muscle relaxation.

The length of the NGT necessary to reach the stomach was assessed before insertion to detect knotting during attempted insertion. The length of the tube necessary to reach the stomach was calculated by placing the tip of the NGT on the patient's xiphoid process and extending it to the tip of his/her nose and over the earlobe.¹⁴ The patients' nostrils were prepared with phenylephrine (0.5%) 5 min before NGT insertion; fentanyl 1 $\mu\text{g}/\text{kg}$ was administered 3 min before inserting the NGT. Immediately before insertion, 3 mL of a water-soluble lubricant jelly was squirted in the patient's nostril.

The patients were divided into 2 groups (control and GlideScope) using computerized random allocation software.¹⁵ A single anesthesiologist was responsible for inserting the NGTs in both groups. Oropharyngeal suctioning was performed in all patients. Whereas no assisting device was used in the control group, the blade of the GlideScope was inserted into the patients' mouths in the GlideScope group. With the aid of the GlideScope blade, the tracheal tube and the tongue were lifted to provide the physician with the best view of the pharyngeal area.

The GlideScope videolaryngoscope (GVL-215) is a reusable device that consists of a handle and a blade (blade length [tip to handle]: 82 mm; thickness [maximum]: 14.5 mm). Although the handle is similar to that of a standard laryngoscope, the blade is different because it is not detachable, has a maximum width of 19 mm at any point, and has a 60° curvature in the midline. A digital video camera with 2 light emitting diodes on either side is embedded in the tip of the blade. The camera has a wide-angle lens and is equipped with an antifogging device; the image captured by the camera is displayed on a 7-in. liquid crystal display color monitor.^{16,17}

In both patient groups, the NGT was passed via the patient's nare posteriorly along the floor of the nose.

Thereafter, the cuff of the tracheal tube was released and the NGT was gently advanced while the patient's chin was lifted. Monitoring was performed for both groups during the procedure, aiming to maintain the patients' bispectral index (Cerebral State Monitor, Danmeter A/S, Odense, Denmark) between 40 and 50. Before NGT insertion, complete neuromuscular block was documented by the absence of evoked responses to train-of-four neurostimulation. A successful NGT insertion was defined as the successful passage of the tube in no more than 3 attempts. It should be noted that during laparotomy procedures, the correct placement of the NGT in both groups was confirmed manually by the surgeon; however, in cases in which manual palpation was not possible, either auscultation or suctioning of stomach secretions were used to confirm appropriate placement. When the NGT was not inserted successfully after 3 attempts, the patient was classified as a procedure failure. In these cases, the NGT was reinserted using a Macintosh laryngoscope and a Magill forceps in the control group and with the help of a Magill forceps in the GlideScope group. The occurrence of complications such as mucosal injury and hemorrhage during the procedure was recorded.

The number of NGT insertion attempts was recorded; every repositioning of the NGT, whether to advance it farther into the stomach or to remove a kink, was recorded as an attempt. The duration required for placement was measured from the time when the tube was advanced into the nostril until confirmation of its successful placement into the stomach. When several attempts were needed, the NGT manipulation times were summed, but the times between manipulations were omitted. An individual unaffiliated with the study or its objectives calculated the times. The rate of successful NGT insertion and the duration necessary for successful NGT insertion were compared between the 2 groups.

The sample size was calculated using STATA 9.1 (StataCorp LP, College Station, TX). Based on data from our pilot study, the mean time for NGT insertion in the 2 groups was 11 \pm 3.6 vs 33 \pm 11.4 (mean \pm SD) seconds in the GlideScope and control group, respectively. A minimum sample size of 4 subjects per group was estimated at $\alpha = 0.05$ and $1 - \beta = 0.95$; 40 patients were included in each group.

Data were analyzed with SPSS v.13 (SPSS, Chicago, IL); Fisher's exact tests, χ^2 , and *t*-tests were used for statistical analyses where appropriate. $P < 0.05$ was considered statistically significant.

The anesthesiologist responsible for inserting the NGT was not blinded to the type of intervention, and this potentially increased the investigator's evaluation bias. To evaluate this bias, we assumed that the investigator might add a maximum of 5 s extra time to the control group when he/she is not blinded to the type of intervention. We used the formula provided

Table 1. Demographic Data of the Patients Studied in Each Group

| | GlideScope group | Blind group | P |
|----------------------|------------------|--------------|-------|
| Age | 55.2 ± 11.9 | 53.33 ± 19.1 | 0.097 |
| Weight | 67.45 ± 8.3 | 69.86 ± 5.7 | 0.118 |
| Gender (male/female) | 22/18 | 22/18 | 1.000 |

by DeLucca et al.¹⁸ to estimate the actual level of difference based on the calculated nominal level.

RESULTS

Eighty patients were enrolled in the study. There was no significant difference in age, gender, and weight of patients enrolled in either group (Table 1). The NGT was not placed successfully within 3 attempts in 4 of the control group patients and in 1 patient in the GlideScope group. These patients were considered treatment failures ($P = 0.35$) and were then successfully treated by adding a laryngoscope (control group) and Magill forceps (both groups) to assist in the next placement attempt. In the control group, the NGT was successfully inserted in the first, second, and third attempts in 23, 4, and 9 patients, respectively. In the GlideScope group, the first, second, and third attempts were successful in 34, 1, and 4 patients, respectively. The first attempt for inserting the tube was successful in the majority of patients in the GlideScope group (34 vs 23, $P = 0.007$).

The mean intubation time in the control group was 38.6 ± 29 s (ranging between 10 and 134 s), whereas that of the GlideScope group was 10.9 ± 9 s (except in 1 case [56 s], whereas intubation time was <22 s in all other cases). The difference between the mean intubation time between the 2 groups was statistically significant (mean difference: 27.7 ± 21 s, 95% confidence interval: 17.7–37.8 s). Estimating the nominal level of the P value as 0.001 and assuming 5 s of extra time that a nonblinded investigator might add to the control group, the actual level of P was defined as <0.02 for statistical significance.¹⁸

The NGTs were inserted without difficulty in the majority of patients; however, complications such as pharyngeal bleeding or mucosal injury were reported in 14 patients (35%) and 8 patients (20%) in the control and GlideScope groups, respectively ($P = \text{NS}$). There were no instances of inadvertent placement of the NGT into the trachea in any group.

DISCUSSION

NGT placement is a procedure that can be difficult for practitioners and may cause trauma to the patient. The incidence of complications (such as nasal and pharyngeal mucosal injuries) from NGT insertion increases with the number of attempts.⁴ Esophageal perforation is another complication associated with NGT insertion.¹⁹ Visualization during attempted NGT

insertion may be beneficial. Jones et al.¹² developed a technique of NGT insertion under direct vision using a bronchoscope specifically for patients with basal skull fractures. Gombar et al.¹ modified the technique of using laryngoscopy with Magill forceps to aid insertion of an NGT and considered the new procedure to be safe, easy, and atraumatic. Scholtes¹¹ similarly reported that the use of a rigid Rusch-guide catheter (normally used for tracheal intubation) may allow placement of a small-diameter NGT in a patient with a small mouth opening in whom manipulation of Magill forceps is difficult. This method was also reported to be associated with fewer hemodynamic changes compared with laryngoscopy, regardless of the duration of the procedure.¹¹ Lai et al.² reported that the GlideScope, originally designed to improve visualization of the glottis, facilitated NGT placement in 5 consecutive, tracheally intubated patients. Hunter and Cohen¹³ reported a case in which the GlideScope was used to place an NGT after all other methods had failed. St. Laurent et al.²⁰ also used a GlideScope to insert a transesophageal echocardiography probe in 2 difficult cases.

According to the statistical analysis of this study, NGT insertion with the assistance of a GlideScope was performed in a shorter time but with similar failure rates. Moreover, the first attempt to insert the NGT was successful in the majority (85%) of patients using this method. As a result, we conclude that the GlideScope is superior to the blind technique in patients with normal airway anatomy.

It should be noted that a single physician was responsible for inserting all NGTs in this study, aiming to reduce skill bias. This person was not blinded to the intervention group, and this increased the potential investigator evaluation bias. In future studies, it would be beneficial to have multiple physicians insert the NGTs and to use independent observers to time procedure duration. To evaluate investigator bias, the actual level was calculated based on the nominal level. In addition, the use of a laryngoscope and Magill forceps was the routine rescue technique in our center, and, in view of the fact that this is the first trial to assess the efficacy of GlideScope for NGT insertion, we used the laryngoscope in the control group failed cases. Although the rescue techniques were successful in all failed cases, it is possible that using the GlideScope and Magill forceps as the single rescue technique in both groups would have provided us with more accurate results.

GlideScope can improve NGT insertion speed and potentially reduce complications in anesthetized patients; however, considering the fact that the sample size of the study was calculated based on the mean intubation time reported during the pilot study, we acknowledge that this sample size is not sufficient to unequivocally reject the null hypothesis regarding the success and complication rates. Additionally, patients with difficult airways were excluded from this study;

therefore, further studies with larger sample sizes, including difficult cases, are recommended.

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Early Use of Eyeglasses for Myopia Predicts Long Axial Length of the Eye

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Patients with long axial length (AL) eyes (>25 mm) are at increased risk of globe perforation during performance of intraconal (retrobulbar) eye block. These patients often require glasses or contact lenses for myopia (nearsightedness) as children or young adults. A history of early correction for myopia might, therefore, be a predictor of long AL eyes. One hundred one patients undergoing cataract surgery had AL measured and answered questions about their use of corrective lenses. We found that a history of correction for myopia as a child or young adult was 82% sensitive and 84% specific for having a measured AL \geq 25 mm. Patients with this history may be at increased risk for globe perforation during intraconal block.

(Anesth Analg 2010;110:119-21)

The intraconal (retrobulbar) block technique is still used commonly for ophthalmic surgery. A rare but serious complication of intraconal block is globe perforation.¹ Patients with long axial length (AL) eyes (>25 mm) are at increased risk of having this complication,^{2,3} and the risk seems to increase as AL increases.²⁻⁴ Measurement of AL (usually accomplished by ultrasound) is not obtained before many eye operations, although it is routinely obtained before cataract surgery to help determine the appropriate lens for implantation. It has been proposed by Dr. Gary Fanning, an ophthalmic anesthesiologist, that a history of wearing glasses for myopia as a child or young adult might be a useful screening tool for detecting patients with long AL eyes when ultrasound measurement is not available.⁵ This study was undertaken to test this hypothesis.

METHODS

With approval of the Massachusetts Eye and Ear Infirmary IRB, written informed consent was obtained from adults, aged 18 yr and older, scheduled for

elective cataract surgery. Patients were excluded who lacked preoperative AL measurement, had a history of ocular trauma or other known anatomic abnormality of the operative eye, or were unable to communicate. Each patient was studied only once.

The protocol was a third-party blind design. A nurse who was blinded to the AL measurement gave subjects a brief questionnaire to collect demographic information (age, gender, eye being operated on) and answers to the following questions:

1. Did you wear glasses or contact lenses as a child or young adult?
2. If so, at approximately what age did you start to wear glasses?
3. If you wore glasses or contact lenses, what was the reason?
 - a. Nearsightedness (difficulty seeing things at a distance) or a combination of nearsightedness and another eye condition(s)?
 - b. Some other eye condition?
 - c. Unknown or unsure?

One of the authors (JB) obtained the AL of the operative eye from the patient's preoperative ultrasound report. The AL and questionnaire data were stored separately, and the two databases were not combined until study enrollment was complete.

Statistics

A "positive" response was defined as the report by the patient of using glasses or contact lenses as a child or young adult for myopia, with or without another eye condition requiring glasses or contact lenses. There were no previous data relating age of correction to AL, so we accepted ages up to 30 yr as "young adult." "Long AL" was prospectively defined as AL \geq 25 mm.

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Table 1. Summary Data

| | |
|---|-----------------|
| Gender (M/F) | 43/58 |
| Operative site (right eye/left eye) | 44/57 |
| Age \pm SD (yr) | 70 \pm 12 |
| Axial length \pm SD (mm) | 24.3 \pm 2.07 |
| Axial length \geq 25 mm (no./total) | 28/101 |
| Glasses for myopia as child (no./total) | 35/101 |

Table 2. Axial Length in 35 Patients With Positive Response on Questionnaire

| Axial length (mm) | No. patients (%) |
|-------------------|------------------|
| \geq 25 | 23 (66) |
| 24–24.9 | 7 (20) |
| 23–23.9 | 3 (9) |
| 22–22.9 | 2 (5) |

Table 3. Sensitivity and Specificity of Positive Response on Questionnaire

| Axial length (mm) | Sensitivity | Specificity |
|-------------------|-------------|-------------|
| \geq 25 | 82 (23/28) | 84 (61/73) |
| \geq 26 | 88 (15/17) | 76 (64/84) |
| \geq 27 | 89 (8/9) | 71 (65/92) |
| \geq 28 | 100 (5/5) | 69 (66/96) |

Sensitivity of a "yes" answer = True positives/(true positives + false negatives).

Specificity of a "no" answer = True negatives/(true negatives + false positives).

Quantal data were analyzed with χ^2 , and continuous variables with unpaired *t*-tests. A logistic regression model was used to quantify the relationship between AL \geq 25 mm and the age at which glasses or contact lenses were first worn. $P < 0.05$ (two-sided) was considered statistically significant. Based on our estimated effect size of 50% difference in percentage of patients having long AL (30% in control versus 80% in cases, case-control ratio 1:2), enrollment of 100 patients was calculated to provide $>90\%$ power to find a significant association between AL and a positive response with 5% Type I error.

RESULTS

There were 101 subjects enrolled, and data from all subjects are included in the analysis. For two subjects, the age at first wearing glasses could only be recalled as a grade in secondary school, and this was replaced with an age estimate. The summary data are listed in Table 1.

Twenty-eight of the 101 patients (28%) had long AL of these, 23 (82%) had a positive response to the questionnaire ($P < 0.0001$). Of the 35 patients with a positive response, 23 had long AL (66%), and most of the remaining 12 patients had borderline long AL (Table 2).

Five patients had long AL but did not have a positive response. The AL measurements for these patients were: 25.1 (2 patients), 25.2, 26.4, and 27.6 mm (one patient each). The sensitivities and specificities of positive and negative responses at various AL are listed in Table 3. The relationship between the length

of the eye and the age at which a patient started to wear glasses or contact lens for myopia did not reach statistical significance ($P = 0.07$).

DISCUSSION

This study demonstrates that a history of wearing glasses or contact lenses for myopia at an early age is a fairly sensitive and specific test for detecting patients with long AL eyes. Moreover, the sensitivity increased as the AL increased. The study did not prove that this positive history is associated with an increased risk of globe perforation during intraconal block, but previous studies suggest an association between myopia and globe perforation from intraconal blocks.^{2–4} Myopic eyes extend further posteriorly into the intraconal space than normal eyes, and highly myopic eyes (AL >29 mm) have a high incidence of posterior staphyloma.⁶ These abnormalities increase the chance of a block needle inadvertently perforating the posterior portion of the globe when it enters the intraconal space. Two retrospective studies suggest the risk of globe perforation increases when the AL is longer than 25–26 mm,^{2,3} but no study has defined a specific AL beyond which the risk becomes unacceptable. The age at which a patient started to use glasses in our study was not significantly related to AL, but the association was statistically borderline significant and it is likely that the subgroup analysis was under-powered to make this determination. For many eye operations AL measurements are not performed routinely, and it would be useful to have some other estimate of AL before administering an orbital block. One possibility is the eyeglass prescription, if available. Spherical equivalent is the first number in an eyeglass prescription (measured in units of diopters), and a negative number denotes myopia. Patients with a spherical equivalent more negative than about -5 diopters are likely to have AL >25 mm, and AL has been shown to increase in a nearly linear fashion with increasingly negative spherical equivalents.⁷ In the absence of information about the prescription, a history of wearing eyeglasses for myopia is easy to elicit and also has a strong association with long AL. If long AL is suspected from this history, before performing an intraconal block, we believe consideration should be given to obtaining a more exact measurement of AL. If intraconal block is still indicated, the angle of the approach to the intraconal space should be altered to reduce the risk of striking the elongated globe. Alternatively, one could (and perhaps, for high myopes, one should) substitute a local anesthetic technique that is associated with a lower risk of globe injury (e.g., topical, subconjunctival, intracameral/topical, sub-Tenon's, or extraconal)⁸ or general anesthesia.

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Lateral Antebrachial Cutaneous Neuropathy as a Result of Positioning While Under General Anesthesia

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As the second most common cause for professional liability in anesthetic practice, nerve injuries are a well-recognized complication. We present a case of lateral antebrachial cutaneous neuropathy after prolonged general anesthesia for left medial meniscal transplant and microfracture surgery. In the orthopedic and sports medicine literature, <100 cases have been described. We discuss the possible causes and propose surgical positioning as the most likely cause of postoperative lateral antebrachial cutaneous neuropathy in our patient.

(Anesth Analg 2010;110:122-4)

As the second most common cause for professional liability in anesthetic practice, nerve injuries are a well-recognized complication.¹ Injury to the lateral antebrachial cutaneous nerve (LABCN), which innervates the radial forearm, has been reported to arise from repetitive forceful pronation in throwing athletes; excessive strenuous upper extremity exercise; antecubital phlebotomy; and compression due to a tourniquet, restraining strap, or improperly placed blood pressure cuff.² We present a case of lateral antebrachial cutaneous neuropathy after prolonged general anesthesia in supine position.

CASE DESCRIPTION

A 25-yr-old man (111 kg, 211 cm) presented for left medial meniscal transplant and microfracture surgery. The patient was otherwise healthy, ASA physical status I. He was placed under general anesthesia in supine position for the 6-h procedure. The blood pressure cuff was placed on the right arm with a 5-min cycling interval, and both upper extremities were supinated and secured to padded arm boards with <90° abduction. Upon emergence, the patient complained of significant postoperative pain for which a femoral nerve catheter was placed. Upon alleviation of the pain, the patient began complaining of right arm weakness and intermittent paresthesia. Further evaluation and examination found his motor strength to be 4/5 with initial attempts at arm flexion (weakness secondary to pain per patient report) and 5/5 after 90° flexion at the elbow. Passive arm extension was also difficult for the patient secondary to pain. Forearm pronation and supination were intact, although the patient did complain of pain with supination. Wrist flexors and extensors were without deficit. His grip strength was 5/5. On sensory examination, there was distinct anesthesia and paresthesia over the lateral forearm

extending to the lateral thumb and nail bed. Positive Tinel sign was demonstrated over the antecubital fossa. The distribution of the patient's sensory deficit is illustrated in Figure 1. The patient denied any history of recent antecubital phlebotomy. On postoperative day 1, his symptoms were improved but still present. He was advised to apply ice, rest the arm, take nonsteroidal antiinflammatory drugs at the discretion of his orthopedic surgeon, and follow up with the Anesthesiology Department if his symptoms did not improve. The patient was discharged on postoperative day 2. Follow-up by the Department of Anesthesiology was conducted on postoperative day 4 via telephone, at which time the patient noted complete resolution of his symptoms. He reported taking only oral hydrocodone/acetaminophen and aspirin after hospital discharge, while applying ice and resting the extremity. The patient provided verbal permission to report the case, but written permission was not obtained because the patient could not be contacted at the time of case submission.

DISCUSSION

The musculocutaneous nerve originates from the C5-8 nerve roots and is the terminal branch of the lateral cord of the brachial plexus. The nerve travels deep in the anterior compartment of the arm to innervate flexor compartments, and it gives off motor branches between the biceps and brachialis muscles. Although there are anatomic variations, the nerve usually becomes superficial just lateral to the biceps tendon where it penetrates the brachial fascia at the level of the elbow. Remaining sensory fibers coalesce to form the LABCN and provide sensation to the radial half of the forearm.³⁻⁵

Isolated musculocutaneous nerve injuries caused by strenuous activity or exercise, playing various sports, and poor surgical positioning usually involving prolonged abduction, extension, and external rotation at the shoulder have been reported in the literature. For example, this type of nerve injury is often seen after patient positioning when there is a significant height discrepancy between the taller surgical table and shorter arm boards.^{4,6-8} Lateral antebrachial cutaneous neuropathy is uncommon and often misdiagnosed.

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Figure 1. An illustration of the pattern of sensory deficits displayed by our patient.

A differential diagnosis of lateral antebrachial cutaneous neuropathy involves excluding cervical radiculopathy, lateral epicondylitis, radial tunnel and pronator teres syndromes, biceps tendonitis, brachial plexus injury, and median or radial nerve injury.^{7,9} The constellation of symptoms characterizes the level at which the lesion exists. Complete loss of biceps and brachialis strength signifies a high lesion or musculocutaneous nerve injury. If the injury occurs within or just below the coracobrachialis muscle, the patient will exhibit biceps brachii and brachialis weakness with radial forearm paresthesias. An injury at the level of the elbow with pure sensory manifestation signifies an LABCN injury. These patients often complain of lateral forearm paresthesia without motor deficit.^{4,5,7,9} Diagnosis of an LABCN injury can often be suggested on the basis of history and physical examination; however, electromyography or nerve conduction studies are required for definitive diagnosis.^{5,8} For instance, a case of brachial plexopathy masquerading as an LABCN injury was reported involving a soldier carrying a 60-lb rucksack; electromyography and nerve conduction studies confirmed the true diagnosis.¹⁰ Because our patient recovered in such a timely manner, we were unable to conduct the studies required to provide a definitive diagnosis of LABCN injury.

Interestingly, although our patient complained of paresthesia in the classical distribution of the LABCN, his symptoms also extended to include a strip of skin on the dorsum of the thumb. The 3 nerves that innervate the dorsal hand are well described: the superficial branch of the radial nerve; the dorsal branch of the ulnar nerve; and the LABCN. With variability found to be the rule, several studies have demonstrated a high frequency of overlapping patterns of sensory innervation of the dorsal thumb. Mackinnon and Dellon¹¹ found overlapping innervation of the LABCN and the superficial branch of the radial nerve 70% of the time. Mok et al.¹² demonstrated an actual

intraneural connection between the 2 nerves in 33% of cadavers. Overlapping innervation likely explains the distal extent of our patient's symptoms.

We propose patient positioning leading to compression or stretch of the LABCN as the most likely cause of postoperative lateral antebrachial cutaneous neuropathy in our patient. Other etiologies for injury to the LABCN include repetitive forceful pronation as seen in throwing; excessive strenuous upper extremity activity or exercise; windsurfing with a flexed arm; antecubital phlebotomy; and compression due to a tourniquet, restraining strap, or improperly placed blood pressure cuff.^{2,13} Phlebotomists are encouraged to avoid needle sticks in the medial portion of the antecubital fossa to avoid injuring the medial antebrachial cutaneous nerve, and there are published case reports documenting lateral antebrachial cutaneous neuropathy after such a procedure on the lateral aspect of the arm.^{14,15} Although our patient denied antecubital phlebotomy, this is an important etiology to consider. There was 1 case report of nerve injury due to a frequently cycled blood pressure cuff, but this seems to be exceedingly rare and was reported to involve the radial nerve.¹⁶ Additional blood pressure cuff injuries are also reported in the literature, although these involved skin necrosis and a humeral fracture.^{17,18} Our patient had an adult blood pressure cuff sized appropriately by a cuff width measuring approximately 40% of the arm circumference and a bladder length encircling more than 50% of the arm circumference. The cycling interval for blood pressure cuff inflation was the maximal allowable interval time of 5 min for a patient undergoing a general anesthetic. The automated oscillometric pneumatic cuff used in our facility minimizes the risk for nerve damage by inflating to a pressure just above the arterial occlusion pressure from the previously measured arterial blood pressure. Although injury caused by a blood pressure cuff cannot be completely excluded, studies evaluating muscular and nerve injuries caused by tourniquet compression implicate high tourniquet pressures in excess of 200 mm Hg with the radial nerve being the most frequently injured.¹⁹ We believe that tourniquet injury due to blood pressure cuff inflation was an unlikely cause of LABCN injury in our patient.

As described by Belzile and Cloutier⁵ and illustrated in Figure 2 by Naam and Massoud,⁸ the LABCN is easily compressed at the level of the biceps tendon in particularly thin or muscular patients. This compression is exaggerated with prolonged supination. Our patient was positioned supine, with bilateral upper extremities supinated and abducted $<90^\circ$ without flexion at the elbow. The arms were secured to padded arm boards in this position. Our patient was 111 kg and 211 cm with a muscular build. When asked on postoperative assessment if complete extension of his unaffected arm was comfortable, the patient reported that he felt strained while in complete extension and more comfortable with a slight degree of

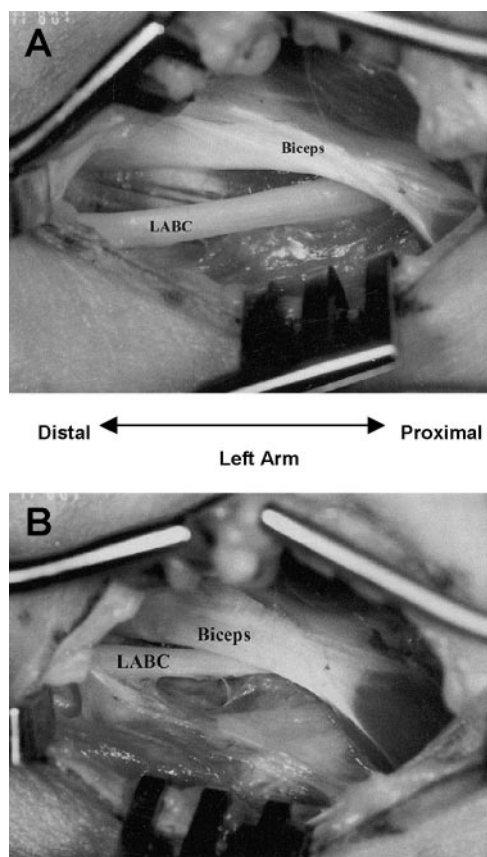


Figure 2. Gross dissection of the lateral antebrachial cutaneous nerve (LABCN; labeled LABC in the figure), with the extremity pronated (A) and supinated (B). (Reprinted from Naam and Massoud,⁸ with permission from Elsevier Ltd.)

flexion at the elbow. As both arms were positioned similarly, we cannot explain why 1 arm was symptomatic and the other was unaffected. However, we believe that positioning was responsible for the unilateral LABCN injury our patient experienced.

Proper positioning for patients undergoing general anesthesia is key to protecting patients from peripheral nerve injuries, particularly during prolonged procedures. As Coppieters et al.²⁰ and the American Society of Anesthesiologists Task Force on Prevention of Perioperative Peripheral Neuropathies²¹ suggest, after a thorough preoperative history and physical examination, the ideal positioning should include minimal shoulder abduction, extension, and external rotation, the head should remain midline, elbows should be slightly flexed with forearm supination, and the wrists should remain neutral. Although elbow flexion is typically performed to decrease tension on the median nerve, it would also decrease tension at the level of the antecubital fossa where the LABCN passes beneath the biceps tendon. Preoperative assessment of the patient's comfort in the anticipated surgical position is prudent practice. Our patient's injury likely could have been avoided if we had assessed his

comfort preoperatively and positioned his elbows slightly flexed as opposed to fully extended.

Fortunately, our patient's symptoms resolved completely within 4 days using only rest of the extremity, opioids, and nonsteroidal antiinflammatory drugs. Treatment options for LABCN injury include rest of the extremity, posterior splinting, nonsteroidal antiinflammatory drugs, steroidal injection, ultrasound, transcutaneous electrical nerve stimulation, and surgical decompression for refractory cases.⁵

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The Use of the Behavioral Pain Scale to Assess Pain in Conscious Sedated Patients

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BACKGROUND: Assessing pain in mechanically ventilated critically ill patients is a great challenge. There is a need for an adequate pain measurement tool for use in conscious sedated patients because of their questionable communicative abilities. In this study, we evaluated the use of the Behavioral Pain Scale (BPS) in conscious sedated patients in comparison with its use in deeply sedated patients, for whom the BPS was developed. Additionally, in conscious sedated patients, the combination of the BPS and the patient-rated Verbal Rating Scale (VRS-4) was evaluated.

METHODS: We performed a prospective evaluation study in 80 nonparalyzed critically ill adult intensive care unit patients. Over 2 mo, nurses performed 175 observation series: 126 in deeply sedated patients and 49 in conscious sedated patients. Each observation series consisted of BPS ratings (range 3–12) at 4 points: at rest, during a nonpainful procedure, at retest rest, and during a routine painful procedure. Patients in the conscious sedated state also self-reported their pain using the 4-point VRS-4.

RESULTS: BPS scores during painful procedures were significantly higher than those at rest, both in deeply sedated patients (5.1 [4.8–5.5] vs 3.4 [3.3–3.5], respectively) and conscious sedated patients (5.4 [4.9–5.9] vs 3.8 [3.5–4.1], respectively) (mean [95% confidence interval]). For both groups, scores obtained during the nonpainful procedure and at rest did not significantly differ. There was a strong correlation between nurses' BPS ratings and conscious sedated patients' VRS-4 ratings during the painful procedure ($r_s = 0.67$, $P < 0.001$). At rest and during nonpainful procedures, 98% of the observations were rated as acceptable pain (VRS 1 or 2) by both nurses and patients. During painful procedures, nurses rated the pain higher than patients did in 16% of the observations and lower in 12% of the observations.

CONCLUSION: The BPS is a valid tool for measuring pain in conscious sedated patients during painful procedures. Thus, for noncommunicative and mechanically ventilated patients, it may be regarded as a bridge between the observational scale used by nurses and the VRS-4 used by patients who are able to self-report pain.

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Many critically ill patients in the intensive care unit (ICU) suffer from pain,^{1–3} notably those on mechanical ventilation.^{4,5} From 35% to 55% of nurses have been reported to underrate patients' pain,^{6,7} and a current practices study revealed that the observed rates of assessment during procedural pain in mechanically ventilated patients remain below 40%.⁸ Researchers have recognized that pain and inadequate pain relief are major causes of physiological adversity and emotional stress.^{9–11} Therefore, it would seem important to achieve

effective management of analgesia, first by measuring pain in a valid and reliable manner.

Various pain scales are available, but there is insufficient evidence of their reliability in the diverse ICU population. The Society of Critical Care Medicine recommends self-reporting by communicative patients using the numerical rating scale (NRS, range 0–10).⁷ This scale requires a certain level of comprehension, so one may opt for an alternative, the 4-point Verbal Rating Scale (VRS-4), which has shown good reliability and validity.¹² Postoperative patients even prefer the VRS-4 over the NRS because of its ease of use.¹²

The observational Behavioral Pain Scale (BPS, range 3–12), applied by nurses, has been validated in deeply sedated, mechanically ventilated patients.^{13,14} It is composed of 3 subscales: facial expression,^{1–4} movement of the upper limbs,^{1–4} and compliance with mechanical ventilation.^{1–4,13} The BPS reflects objective visible behavior at 1 specific time point, whereas the NRS represents a global impression of pain, including several contextual factors during a longer time period.¹⁵ Gélinas et al.¹⁶ developed the Critical Care Pain Observation Tool (range 0–8). Based on the BPS, the

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Critical Care Pain Observation Tool has not yet been tested among different critical care populations and requires additional validation.¹⁷

Apart from communicative and deeply sedated patients, a third group can be identified, i.e., conscious sedated mechanically ventilated patients. Current ICU practice strives to restrict sedation to a conscious level whenever possible, in agreement with the landmark report¹⁸ that showed that ventilated patients benefit from daily interruption of sedative infusions. Ventilation could be stopped earlier in these patients, resulting in shorter ICU stays, and they showed no adverse psychosocial outcomes.¹⁹

Self-reporting using the NRS or VRS-4 may be complicated or unreliable in these patients because of their temporarily limited capacities of abstraction and concentration, and lack of comprehension.^{7,11} Furthermore, the BPS has been validated only in deeply sedated and noncommunicative patients.

For this growing group of conscious sedated patients, an observational pain scale such as the BPS, which can be used by the nurse, can add value to VRS-4 scores, because patients' self-reporting may be complicated and/or unreliable. Therefore, we designed a study to compare use of the BPS_{nurse} in conscious sedated patients and in deeply sedated patients, for whom the BPS was developed. Additionally, in conscious sedated patients, the combination of the BPS_{nurse} and the patient-rated VRS-4 was evaluated.

METHODS

Design

A prospective, observational study was performed in a 30-bed surgical/medical ICU in a teaching hospital in Nieuwegein, The Netherlands. The Medical Ethical Committee of the St. Antonius Hospital approved the study protocol and waived the need for informed consent because the observational study design and pain measurements are considered as standard care.

Patients and Classifications

During the 2-mo study period, all patients admitted to the ICU were evaluated for inclusion in the study once a day (between 8:00 AM and 12 noon). ICU patients who were 18 yr and older, sedated irrespective of sedation depth, and ventilated for at least 8 h before assessment were eligible for inclusion. Patients who received neuromuscular blocking medications or muscle-paralyzing drugs, who were unconscious after resuscitation, quadriplegic, had a critical illness (poly) neuropathy, or had an epidural catheter, were excluded.

Included patients were classified as "sedated" or "conscious sedated" on the specific day. Sedated patients were defined as patients who were not able to communicate during all 4 consecutive assessments (at rest, during nonpainful procedures, at retest rest, and during painful procedures) on that particular day.

Table 1. The Behavioral Pain Scale¹³

| Item | Description | Score |
|-----------------------------|--|-------|
| Facial expression | Relaxed | 1 |
| | Partially tightened | 2 |
| | Fully tightened | 3 |
| | Grimacing | 4 |
| Upper limbs | No movement | 1 |
| | Partially bent | 2 |
| | Fully bent with finger flexion | 3 |
| | Permanently retracted | 4 |
| Compliance with ventilation | Tolerating movement | 1 |
| | Coughing but tolerating ventilation for most of the time | 2 |
| | Fighting ventilator | 3 |
| | Unable to control ventilation | 4 |

Conscious sedated patients were defined as patients who were able to communicate during at least part of the assessment. Patients could be included on multiple days, an approach also used in the first BPS validation study in nonresponsive critically ill patients.¹³

Eighty patients were included during the 2-mo study period. Fifty patients were classified as sedated on all study days, 17 as conscious sedated on all study days, and 13 as either sedated or conscious sedated on different days in the study period.

Pain Measurement Instruments

BPS

The BPS is an observational pain scale, preferably applied by the attending nurse. It has been validated for use in deeply sedated, mechanically ventilated patients.^{13,20} Easy to use and well accepted by nurses, the BPS contains 3 subscales: facial expression, upper limb movements, and compliance with mechanical ventilation (Table 1). Each subscale is scored from 1 (no response) to 4 (full response). Therefore, BPS scores range from 3 (no pain) to 12 (maximal pain).¹³ A BPS score of 6 or higher is considered to reflect unacceptable pain.²

VRS-4

The VRS-4 is a 4-point verbal rating scale (range 1–4) used for patient self-reporting. It was adapted from the Verbal Graphic Scale,²¹ which includes 4 categories: 1) free of pain (NRS 0), 2) mild pain (NRS 1–3), 3) moderate pain (NRS 4–6), and 4) severe pain (NRS 7–10). This shorter version was used because conscious sedated patients may temporarily lack full comprehension of the more complex 11-point NRS. Unacceptable pain using the 11-point NRS is defined as NRS >3 (moderate pain and severe pain),^{6,7} thus unacceptable pain using the 4-point VRS was defined as a score of 3 or 4.

In this study, the "BPS_{nurse}" is defined based on a BPS rating by the attending nurse. The "VRS-4_{patient}" is defined by the VRS-4 rating by the patient.

Study Procedures and Intervention

Pain was assessed during 2 routine nursing procedures. One was an arterial catheter dressing change, identified as a nonpainful procedure from a pilot study in our ICU. The second was turning, a procedure that patients have described as painful.^{22,23} In addition, pain was assessed at rest, i.e., before the first of these procedures, and in between these procedures, at least 30 min after the first procedure.

At each of these 4 points, a nurse researcher (AV, critical care nurse and student in nursing sciences) and an attending nurse simultaneously observed the patient for about 1 min, with the observers' assessments made independently. The attending nurse then determined the Ramsay Score (RS). Next, the nurse researcher and the attending nurse independently determined the BPS_{nurse} score. Communicative patients were then asked to apply the VRS-4_{patient}. This order was decided upon to prevent the nurses' scores from being influenced by the patient's score.

Demographic data such as gender, age, intensive care indication, and the Sequential Organ Failure Assessment score²⁴ were collected.

Training

The 72 nurses who participated in the study all attended a 4-h training session, given by a BPS-trained ICU nurse. Attention was given to the essentials of pain and the difficulties of scoring pain in ventilated and sedated patients. The use of the BPS was explained by means of pictures of ICU patients. All received a protocol explaining the study and the BPS.

Depth of Sedation

Depth of sedation was assessed by the RS, which is a single-item, 6-level scale (scores range from 1 to 6).²⁵ The levels are: 1) patient anxious, agitated, restless; 2) patient cooperative, oriented, and tranquil; 3) patient drowsy or asleep, responds easily to commands; 4) patient asleep, brisk response to a light glabellar tap; 5) patient asleep, sluggish response to a light glabellar tap; and 6) patient asleep, no response to a light glabellar tap.⁹ The RSs were rated in the morning (between 7:30 and 8:00 AM), whereas the pain assessments were completed between 8:00 AM and 12:00 noon. In 8 patients, the RS was different during sedation assessment and pain assessment. The RS for the conscious sedated patients (median 6, range 3–6) was significantly lower ($P < 0.001$) than that for the sedated patients (median 3, range 2–5).

Standard Pain and Sedative Medication in the ICU

All patients received pain medication by protocol, i.e., 4 times daily 1 g of acetaminophen rectally, plus either 4 times daily 10 mg morphine subcutaneously if in moderate pain or 30–50 mg morphine per day by continuous IV infusion when in severe pain. Pain severity was evaluated on a daily basis. For procedural pain, patients received either no morphine or a

bolus of 5–10 mg morphine, depending on the attending nurse's judgment. Patients were sedated preferably with propofol or midazolam, according to local standard practice.

Data Analysis

Data were analyzed using the SPSS software (version 15.0, Chicago, IL). The statistical analysis was performed by calculation on all measurements of all patients, including 1 measurement per day per patient. This approach was used by Payen et al.¹³ when they first validated the BPS in nonresponsive critically ill patients and can be justified because a critically ill patient's condition may rapidly change over 24 h, e.g., when taken off mechanical ventilation, with consequences in terms of organ failure, neurological or respiratory situation, sedation levels, pain levels, and communication abilities.

Kappa coefficients with quadratic weights were used to reflect agreement between the nurse researcher and the attending nurse regarding the BPS. Weighted kappa penalizes disagreement in proportion to its severity.²⁶ Theoretically, the value of kappa can range from 0 (no agreement) to 1.0 (perfect agreement). A value larger than 0.6 was regarded as satisfactory.²⁷ The 95% confidence intervals (CIs) for kappa coefficients were calculated.

Internal consistency, a measure of how the items within a scale are interrelated, was expressed in Cronbach's α . A high Cronbach's α value reflects high internal consistency. Generally, a value larger than 0.7 is regarded as satisfactory.²⁸

The effect size is a standardized way to express the magnitude and meaning of an instrument's capacity to change, in this case, the BPS. The effect sizes of the BPS total and BPS items were calculated as the difference between the score at rest and the score during the painful procedure, divided by the standard deviation (SD) at rest.²⁹ An effect size of around 0.20 is generally considered to be small, 1 of 0.50 indicates moderate differences, and those of 0.80 or above indicate large differences.³⁰

Values are expressed as mean and 95% CI. Spearman nonparametric rank correlation coefficients (r_s) were used to measure the degree of correlation for 2 ordinal variables. The unpaired t -test and the Mann-Whitney U -test served to compare differences in quantitative and nonparametric data, respectively. The test-retest procedure was analyzed by the paired Student's t -test. A P value of <0.05 was considered statistically significant.

RESULTS

Patients and Data

Table 2 shows the characteristics of the 80 enrolled patients, classified by state of sedation. The mean amount of propofol administered (\pm SD) was 130.4 \pm 58.8 mg/h for conscious sedated patients vs 175.6 \pm 72.6 mg/h for sedated patients ($P < 0.05$). The mean

Table 2. Baseline Patient Characteristics of All 80 Patients Participating in the Study, with Patients in Sedated State at All Study Days ($n = 50$), Patients in Conscious Sedated State At All Study Days ($n = 17$), and Patients in Either Sedated or Conscious Sedated State on Different Days ($n = 13$)

| | Patients in sedated state on all days | Patients in conscious sedated state on all days | Patients in both states on different days |
|----------------------------------|--|--|--|
| Number of patients | 50 | 17 | 13 |
| Age (yr) (range) | 66 ± 12 | 61 ± 15 | 60 ± 11 |
| Males/females (n) | 30/20 | 12/5 | 7/6 |
| SOFA score (range) | 5 (1–14) | 5 (1–10) | 6 (2–9) |
| Diagnostic categories (n) | | | |
| Cardiac surgery | 22 | 9 | 3 |
| Abdominal surgery | 9 | 6 | 4 |
| TAAA | 5 | 0 | 0 |
| Nonsurgical | 14 | 2 | 6 |

SOFA = Sequential Organ Failure Assessment; TAAA = thoracoabdominal aortic aneurysm.

Table 3. Interrater Reliability of the BPS Total and Separate BPS Items as Evaluated by Nurses in Sedated Patients (126 Observation Series) and Conscious Sedated Patients (49 Observation Series)

| | Kappa | EA (%) | No. observation series |
|----------------------------|------------------|--------|---------------------------|
| Sedated patients | | | |
| BPS total | 0.83 (0.79–0.87) | 67 | 126 |
| BPS facial expression | 0.80 (0.75–0.85) | 82 | 126 |
| BPS upper limb movement | 0.72 (0.64–0.79) | 82 | 126 |
| BPS compliance ventilation | 0.62 (0.52–0.72) | 88 | 126 |
| Conscious sedated patients | | | |
| BPS total | 0.80 (0.72–0.88) | 70 | 49 |
| BPS facial expression | 0.78 (0.69–0.87) | 81 | 49 |
| BPS upper limb movement | 0.67 (0.52–0.82) | 87 | 49 |
| BPS compliance ventilation | 0.61 (0.45–0.70) | 89 | 49 |

EA = exact agreement; BPS = Behavioral Pain Score.

amount of midazolam administered in conscious sedated patients and sedated patients was 3.3 ± 1.2 vs 4.8 ± 2.5 mg/h ($P = 0.32$). The mean ICU stay at time of pain assessment (\pm SD) was 4.5 ± 3.6 for conscious sedated patients vs 5.4 ± 8.1 for sedated patients ($P = 0.43$). One hundred seventy-five observation series were completed: 126 in 63 sedated patients and 49 in 30 conscious sedated patients. The latter also included 49 VRS-4_{patient} scores for 30 patients.

Interrater Reliability

Table 3 gives the quadratic weighted kappa and the exact agreement for the BPS_{nurse} in sedated patients (126 observation series) and conscious sedated patients (49 observation series) between the nurse researcher and the attending nurse. Kappa values were excellent (0.80–0.83). There was no difference in exact agreement for sedated and conscious sedated patients (0.83 [95% CI: 0.76–0.87] vs 0.80 [95% CI: 0.72–0.88]).

Pain Scores in Conscious Sedated Patients and Sedated Patients

BPS_{nurse}

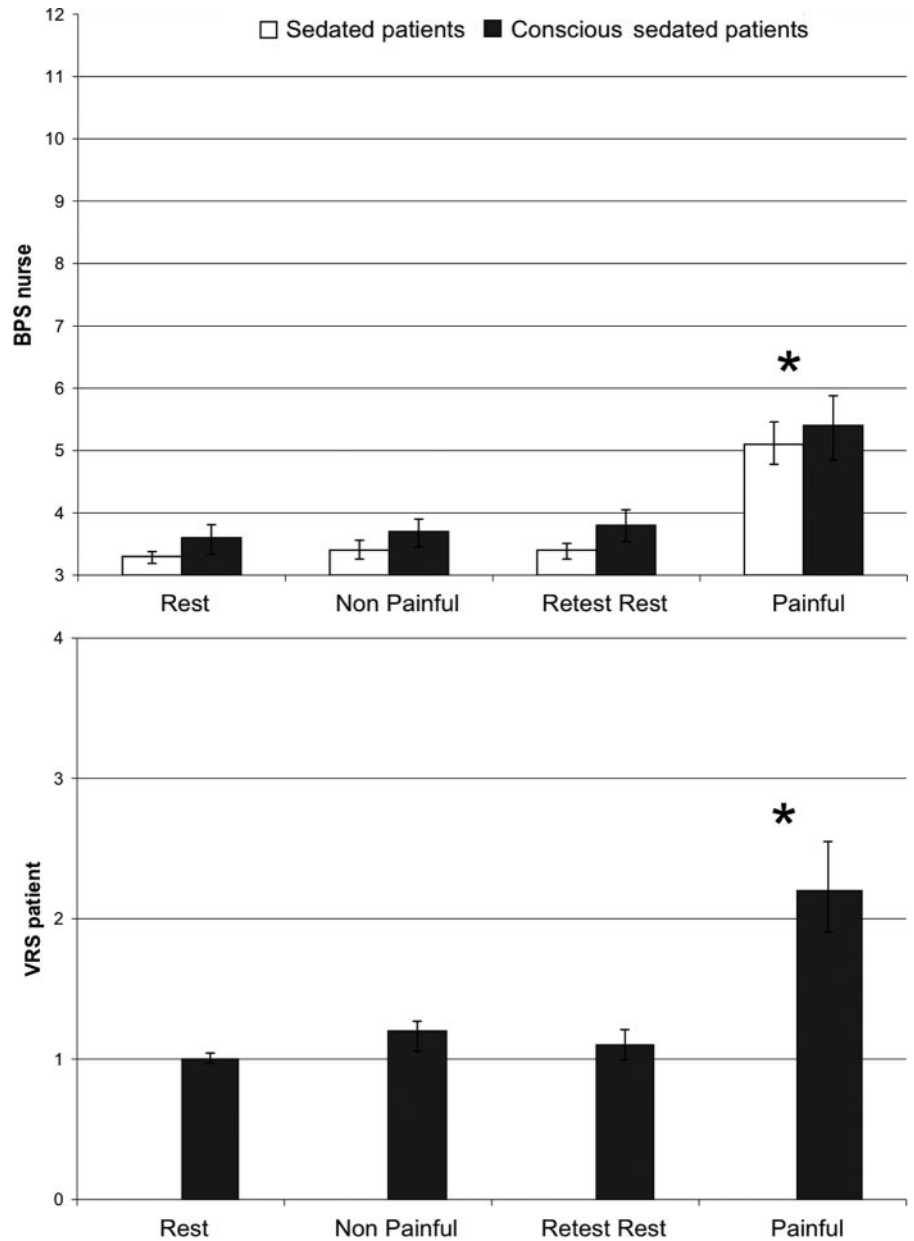
BPS_{nurse} scores were significantly higher during painful procedures than at rest in both sedated patients (5.1 [95% CI: 4.8–5.5] vs 3.4 [95% CI: 3.3–3.5])

and conscious sedated patients (5.4 [95% CI: 4.9–5.9] vs 3.8 [95% CI: 3.5–4.1]) (Fig. 1). There was no difference in BPS_{nurse} scores between the nonpainful procedure and rest in sedated patients (3.4 [95% CI: 3.3–3.6] vs 3.3 [95% CI: 3.2–3.4]) and conscious sedated patients (3.7 [95% CI: 3.5–3.9] vs 3.6 [95% CI: 3.3–3.8]). BPS_{nurse} scores did not differ between sedated patients and conscious sedated patients at rest or during nonpainful or painful procedures.

Table 4 shows that the effect size for responsiveness of BPS total scores was large in sedated patients (126 observation series) and conscious sedated patients (49 observation series) (2.5 and 1.8, respectively). The effect size of the item “facial expression” was largest in both sedated patients (3.6) and conscious sedated patients (2.4). It was also large for “compliance with ventilation” (1.4 and 0.9) but moderate for “upper limbs” in both groups (0.7 and 0.5) (Table 4). During painful procedures, internal consistency was moderate in both sedated patients and conscious sedated patients (Cronbach’s α 0.63 and 0.66, respectively).

VRS-4_{patient}

In conscious sedated patients, VRS-4_{patient} scores were significantly higher during painful procedures



Painful procedure is statistically significant at $P < 0.05$ compared with retest rest

Figure 1. Change in Behavioral Pain Scale (BPS)_{nurse} and Verbal Rating Scale (VRS)-4_{patient} at rest, during nonpainful procedures, at retest rest, and during painful procedures (mean [95% confidence interval]) in sedated patients (126 observation series) and conscious sedated patients (49 observation series).

than at rest (2.2 [95% CI: 1.9–2.5] vs 1.1 [95% CI: 1.0–1.2]). Scores did not differ between the nonpainful procedure and rest (1.0 [95% CI: 1.0–1.0] vs 1.0 [95% CI: 1.0–1.0]).

Comparison Between BPS_{nurse} and VRS-4_{patient} in Conscious Sedated Patients

During the painful procedure, there was a strong positive correlation between BPS_{nurse} and VRS-4_{patient} ($r_s = 0.67$, $P < 0.001$, 49 observation series) (Fig. 2). The 4 boxes in Figure 2 each have been divided into 4 quadrants, separating acceptable pain and unacceptable pain scores (unacceptable pain VRS-4 >2 and BPS >5).

During painful procedures, in 16% of the observations, the patient rated pain as acceptable (VRS scores, 1 or 2), whereas the nurse rated it as unacceptable

(BPS >5). Conversely, in 12% of the observations, the patient rated pain as unacceptable (scores VRS >2), whereas the nurse rated it as acceptable (BPS 3–5). At rest, during the nonpainful procedure, and at retest rest, 98% of the observations were in the quadrant with acceptable pain scores. In these cases, both the patient and the nurse assigned acceptable pain scores.

DISCUSSION

The findings from this study are consistent with the notion that the BPS is reliable for pain assessment in conscious sedated patients. This is of interest in that so far the BPS has been validated for deeply sedated patients only.¹³ All ICU patients recovering from a deeply sedated state will pass through this conscious

Table 4. BPS Total Scores and BPS Items Scores (Mean ± sd) at Rest and During Painful Procedure, with Effect Size in Sedated Patients (126 Observation Series) and Conscious Sedated Patients (49 Observation Series)

| | Retest rest | Painful procedure | P | Effect size |
|----------------------------|-------------|-------------------|--------|-------------|
| Sedated patients | | | | |
| BPS total | 3.4 ± 0.7 | 5.1 ± 1.0 | <0.001 | 2.5 |
| BPS facial expression | 1.1 ± 0.3 | 2.1 ± 1.0 | <0.001 | 3.6 |
| BPS upper limb movement | 1.2 ± 0.4 | 1.4 ± 0.7 | <0.001 | 0.7 |
| BPS compliance ventilation | 1.1 ± 0.4 | 1.6 ± 0.7 | <0.001 | 1.4 |
| Conscious sedated patients | | | | |
| BPS total | 3.8 ± 0.9 | 5.4 ± 1.8 | <0.001 | 1.8 |
| BPS facial expression | 1.1 ± 0.4 | 2.0 ± 1.0 | <0.001 | 2.4 |
| BPS upper limb movement | 1.5 ± 0.6 | 1.8 ± 0.8 | 0.003 | 0.5 |
| BPS compliance ventilation | 1.2 ± 0.4 | 1.6 ± 0.5 | <0.001 | 0.9 |

BPS = Behavioral Pain Score.

sedated state. Thereby, patients who experience agitation or delirium, in whom self-reporting will be complicated, benefit from this pain assessment in the conscious sedated state.

BPS_{nurse} scores during painful procedures were significantly higher than those at rest in both sedated patients and conscious sedated patients. Payen et al.¹³ made a similar observation in deeply sedated patients, i.e., BPS scores were significantly higher for painful procedures such as turning or tracheal suctioning. Therefore, it would seem that the BPS can detect and discriminate pain and is a valid measure of pain in both sedated and conscious sedated patients. Furthermore, the internal consistency was comparable for

observations in both groups, demonstrating similar homogeneity of the items. The fact that the effect size was large in both groups shows that the BPS is able to quantify change in clinical status and detect painful procedures. In both groups, the BPS subscale “facial expression” was the most sensitive to change, as in a previous study.²⁰ The value of facial expression has been proven for both acute and chronic pain not only in adults^{31,32} but also in infants and children.³³

Underestimation of patients’ pain by nurses is a well-known problem.⁵ Surprisingly, using the BPS, nurses also tend to overestimate patients’ pain. On the other hand, conscious sedated patients’ pain scores are not always reliable. Therefore, use of the BPS in combination with the VRS-4 during painful procedures may lead to a more reliable rating of patients’ pain. A previous study from our group³⁴ also concluded that a combination of self-reporting and observational measures is recommended when credibility of self-reporting is doubted. Each method yields unique information. Self-reporting primarily reflects expressive pain behavior that is under control of higher mental processes. Observational measures capture behavior that is less subject to voluntary control and more automatic.³⁴

The level of agreement between the research nurse and the attending nurse was high for both sedated patients and conscious sedated patients (kappa 0.83 and 0.80, respectively). The fact that the kappa values in this study pertained to 72 nurses and generally remained good shows that nurses can be trained to use the BPS in a reliable way in both sedated and conscious sedated patients.

In the ideal study design, nurses would be blinded to the nature of the procedure (painful or nonpainful) that is being performed at the point of assessment. This could be achieved by videotaping the scenes and having the nurses rate the scenes afterward. Care

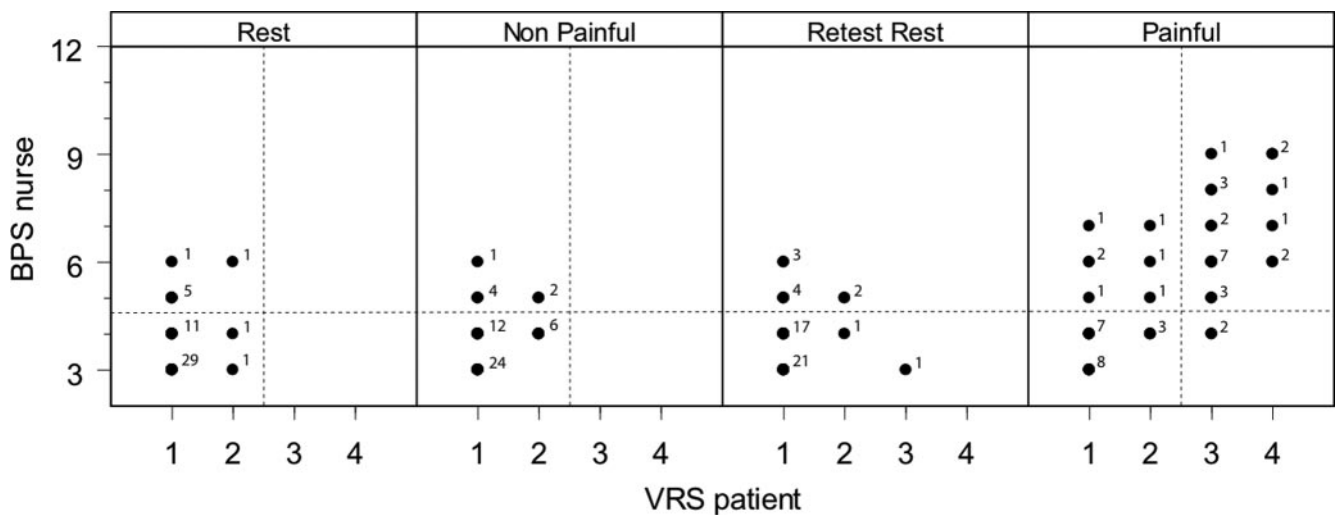


Figure 2. Correlation between Behavioral Pain Scale (BPS)_{nurse} and Verbal Rating Scale (VRS)-4_{patient} (49 observation series) at rest, during nonpainful procedures, at retest rest, and during painful procedures. The dotted line divides acceptable pain scores from unacceptable pain scores (VRS-4 >2 and BPS >5). Each number reflects how many similar results were observed per paired evaluation.

should be taken then to conceal the procedure. A limitation of video recordings is the likelihood that some aspects are missed because the general overview of the patients' situation is necessarily not provided.

In this study, we used the VRS-4 instead of the 11-point NRS because of the lack of capability in conscious sedated patients. This approach was inspired by a study from Briggs and Closs,¹² who showed that postoperative patients prefer the VRS. However, it would be of interest to test whether our assumption that conscious sedated patients are indeed incapable of using an 11-point scale is valid.

In this study, most patients were in a sedated state, although it is desirable for patients to be in a conscious sedated state. This suggests that the health staff should give more attention to the sedation state of the patients in our ICU.

Nevertheless, because the BPS may both overrate and underrate patients' pain, and the patient's self-report is not always reliable, a combination of the nurse-rated BPS and the patient-rated VRS-4 is perhaps ideal for estimating patients' pain. Within this context, patients' sedation levels must be frequently assessed as well, and conscious patients' own self-reported pain scores must be considered the "gold standard."

CONCLUSION

The BPS_{nurse} is valid for use in conscious sedated patients during painful procedures. Thus, the BPS can be regarded as a bridge between the observational scale for noncommunicative and mechanically ventilated patients and the VRS-4 used by patients who are able to self-report pain.

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Development and Validation of Predictors of Respiratory Insufficiency and Mortality Scores: Simple Bedside Additive Scores for Prediction of Ventilation and In-Hospital Mortality in Acute Cervical Spine Injury

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BACKGROUND: Numerous studies have developed a “severity score” or “risk index” for mechanical ventilation and mortality, but there are few to predict outcomes for cervical spine injury (CSI) patients. Our objective in this study was to develop a simple bedside additive predictive score for requirement for ventilation and early in-hospital mortality for patients with CSI.

METHODS: Multivariate logistic regression analysis of the data obtained from 101 patients (development set) after surgical stabilization of traumatic CSI was performed to identify independent predictors of the need for mechanical ventilation and of early in-hospital mortality. Predictors of respiratory insufficiency and mortality (PRIM) scores were developed separately for ventilation and mortality by using the coefficients of the logistic regression model. The model was validated using the receiver operating characteristics curve to test its discriminatory ability and by comparing the predicted and observed outcomes. Validation was performed on an independent data set of 87 consecutive patients (validation set) with traumatic acute CSI.

RESULTS: Mechanical ventilation was required in 16.8% of the patients, and the in-hospital mortality rate was 17.8% in the development set. Independent risk factors for mechanical ventilation were severe injury (American Spinal Injury Association Impairment Scale Grades A and B), breath-holding time, pulmonary infection, hemodynamic instability, and progressive neurologic deterioration. Scores of 15, 20, 25, 25, and 15 were assigned to these variables, respectively. Independent predictors of death were severe injury (American Spinal Injury Association Impairment Scale Grades A and B), hemodynamic instability, progressive neurologic deterioration, and mechanical ventilation. The scores assigned for each of the variables were 20, 20, 40, and 20, respectively. The PRIM scores for mechanical ventilation and mortality had excellent discrimination (area under receiver operating characteristics curve >0.75). There was good correlation between predicted and observed outcomes in the development set and the validation set.

CONCLUSION: PRIM scores enable accurate prediction of individual patient risk of need for mechanical ventilation and in-hospital mortality in association with acute CSI.

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Cervical spinal cord injury (SCI) is a devastating event for the patient and the family. It has a huge impact on society because of the intensive resources required to manage the patient in both the acute and

rehabilitation phases. The risk of mortality associated with cardiorespiratory complications after acute cervical spine injury (ACSI) continues to be distressingly high.¹⁻³ Prediction of individual patient outcomes can be of particular value in clinical decision making and during discussions with patients and families about the prognosis.

Several models have been developed for prediction of postoperative ventilation based on pulmonary function testing, but application of these models to patients with ACSI is not practical, because these patients remain immobilized in supine position. Therefore, prediction of outcome based on simple bedside variables would be more appropriate. No such risk predictor scoring systems are available for patients with CSI. A simple model incorporating clinical features readily identified at bedside and information that could be collected in a relatively short period would permit

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efficient triage and management without waiting for additional tests or results. The objective of this study was to develop and validate a simple bedside additive predictive score for requirement for ventilation and early in-hospital mortality in patients with ACSI.

METHODS

Hospital ethical committee approval was obtained for the study. The study was performed in 2 stages. Stage I included collection of data and identification of predictors of ventilation and in-hospital mortality in patients after surgical stabilization for cervical spine trauma (development set) and development of a predictor score. Stage II included validation of the score on a separate set of data (validation set).

Retrospective record review of patients with blunt CSI who underwent cervical spine surgery under general anesthesia from June 1999 to June 2002 (development set) at our institution (a tertiary referral center with a spinal trauma care facility) was performed. All patients were cared for in the SCI intensive care unit according to the institutional protocols. Data were obtained from the neurosurgical electronic database and anesthesia records, and inconsistencies between the 2 data sources were resolved by hospital record review. Records with incomplete information were excluded from the study. Patients requiring mechanical ventilation or experiencing in-hospital mortality for reasons not related to ACSI were also excluded from analysis. Mortality resulting from refractory spinal shock, respiratory failure, respiratory infections, and deep vein thrombosis (DVT) were considered deaths resulting from SCI. The following data were collected: age, gender, the nature of the injury, the type of cord lesion as seen on magnetic resonance imaging, and the highest level of injury and severity of injury as measured by the American Spinal Injury Association (ASIA) Impairment Scale. Subjects with either motor or sensory neurologic deficits were classified at the highest level of bilateral normal function according to the criteria established by the ASIA Impairment Scale.⁴ Other associated severe injuries such as head injury, rib fractures and lung contusion, abdominal injury, long bone injury, and other comorbid diseases were noted. Presence of preoperative hemodynamic instability (bradycardia or hypotension requiring inotropic support) and respiratory infections, defined by clinical (fever, cough, crepitations, or wheeze) and radiological criteria (new infiltrates and effusion), occurring any time during the hospital stay and deterioration in ASIA scale grade or progression of level of injury after admission were noted. Breath-holding time (BHT), measured as the duration for which the patient could hold their breath after a deep inspiration, was noted as a simple bedside pulmonary function test. Timing of surgical intervention, termed early if undertaken within 3 days of injury, was noted. Immediate postoperative outcome (tracheal extubation

or ventilation), development of postoperative hemodynamic instability, respiratory infections, respiratory insufficiency, and need for postoperative ventilation were noted. The occurrence of DVT, pulmonary embolism, and the mechanical complications of internal orthopedic devices were also noted. Mechanical ventilation was considered an outcome variable if it was required for more than 48 h. The final outcome of interest was in-hospital death or discharge from the hospital. The 2 dependent variables (primary end points) analyzed were requirement for mechanical ventilation due to respiratory insufficiency and in-hospital mortality.

Statistical Analysis

Statistical analysis was performed using SPSS version 13.0 (SPSS, Chicago, IL). Data are expressed as mean and 95% confidence interval (CI) or as proportions (%). Univariate analysis was performed, and predictors were identified separately for mechanical ventilation and in-hospital mortality. All variables with a P value <0.05 in the initial univariate analysis were considered potential predictors of the study primary end points. The significant variables with multiple responses and continuous variables were redefined to obtain a dichotomous response and analyzed again before being entered into the multivariate logistic model. The discriminatory ability of BHT for requirement of mechanical ventilation was tested using receiver operating characteristics (ROC) analysis. The cutoff value with good sensitivity and specificity was determined, and BHT was dichotomized as above and below the cutoff value.

Independent predictors of ventilation and in-hospital mortality were determined using multivariate logistic regression analysis. A hierarchical method of entry was used to intentionally order the variables to be entered. Variables that cannot be altered by clinical intervention, such as the demographic variables, nature and severity of injury at admission, and neurologic deterioration, were entered first into the model. The variables that are affected by intervention, such as hemodynamic instability, BHT, pulmonary infection, and mechanical ventilation, were entered later. The R^2 of the model, change in R^2 obtained by addition of the variable, and the partial coefficients of each variable at each stage at which the variable is added to the equation were determined. The variable was retained if it contributed to a significant change in R^2 (0.5 or more). The final models for predictors of mechanical ventilation and in-hospital mortality were obtained using the variables with statistically significant contributions ($P < 0.05$). The goodness of fit was tested using Hosmer-Lemeshow statistics. A P value >0.05 was considered as showing that the model fits the data.

Development of Predictors of Respiratory Insufficiency and Mortality Scores

The predictor scores were developed separately for mechanical ventilation and in-hospital mortality on

the development set using those variables that were determined to be significant independent predictors during the multivariate analysis. A score proportional to the *B* values, which represent the relative importance and contribution of the variables in the model, was assigned to each of the variables. The weighted average of the variables in the model was set at 100. The scores were then rounded to the nearest 5. The scores thus obtained were referred to as predictors of respiratory insufficiency and mortality (PRIM) scores. The PRIM scores were calculated separately for respiratory insufficiency requiring mechanical ventilation and mortality, using the simple arithmetic sum of the scores of independent end point predictors present in each patient. The discriminative ability of the PRIM scores for mechanical ventilation and in-hospital mortality was calculated by measuring the area under the ROC curve. An area under the ROC curve >0.75 is considered consistent with a good discrimination ability. The best cutoff value of the score that predicts the primary end point was determined from the ROC curves. Finally, the patients in the development set were stratified according to the presence of the predicted mechanical ventilation and mortality. Predicted outcome (mechanical ventilation or in-hospital mortality) obtained with the PRIM scores and observed outcome were compared using the Pearson χ^2 test (with Fisher's exact test where applicable) and the Spearman correlation. The positive predictive value (PPV), negative predictive value (NPV), and accuracy of the scores were determined.

External Validation

External validation was performed on data obtained from an independent data set of consecutive patients with ACSI admitted between June 2002 and August 2005 (validation set). Predicted probabilities of ventilation and in-hospital death for individual patients in the validation set were calculated using the PRIM scores developed. Model discrimination was assessed by ROC curve analysis. The differences in predicted outcome, PPV, NPV, and accuracy were determined as in the development set.

RESULTS

Retrospective data were obtained from 101 patients who underwent surgical stabilization for blunt traumatic CSI and used to derive PRIM scores for respiratory insufficiency requiring mechanical ventilation and mortality. Data for validation of PRIM scores were collected from 87 patients admitted with ACSI.

The baseline demographic and clinical characteristics of the development and validation sets were compared (Appendix, see Supplemental Digital Content, <http://links.lww.com/AA/A40>). Age and percentage of patients with ASIA Grade A, respiratory infection, and hemodynamic instability were significantly higher in the validation set. There were no other significant differences between the data sets in terms

Table 1. Variables Assessed to Determine a Need for Mechanical Ventilation and In-Hospital Mortality in the Development Set

| Variable | Mechanical ventilation | | Mortality | |
|----------------------------|-------------------------|----------|-------------------------|----------|
| | Correlation coefficient | <i>P</i> | Correlation coefficient | <i>P</i> |
| Age | 0.04 | 0.34 | 0.07 | 0.24 |
| Gender | 0.18 | 0.03* | 0.08 | 0.21 |
| Nature of injury | 0.10 | 0.15 | 0.28 | 0.00* |
| Head injury | 0.05 | 0.31 | 0.06 | 0.27 |
| Long bone injury | 0.04 | 0.33 | 0.95 | 0.17 |
| Smoking | 0.40 | 0.34 | 0.05 | 0.30 |
| ASIA grade | 0.36 | 0.00* | 0.32 | 0.00* |
| Severe injury | 0.43 | 0.00* | 0.34 | 0.00* |
| Level of injury | 0.07 | 0.23 | 0.11 | 0.13 |
| Hemodynamic instability | 0.60 | 0.00* | 0.49 | 0.00* |
| BHT | 0.36 | 0.00* | 0.28 | 0.00* |
| BHT (<12 s) | 0.44 | 0.00* | 0.27 | 0.00* |
| Timing of surgery | 0.07 | 0.27 | 0.67 | 0.25 |
| Respiratory infections | 0.66 | 0.00* | 0.56 | 0.00* |
| Neurological deterioration | 0.46 | 0.00* | 0.59 | 0.00* |
| Mechanical ventilation | — | — | 0.69 | 0.00* |

BHT = breath-holding time; ASIA = American Spinal Injury Association.

* Significant correlation between variable and outcome measure.

of demographic and injury characteristics. In the development set, the incidence of respiratory insufficiency requiring ventilation was 16.8%. The overall in-hospital mortality rate was 17.8%. The univariate analysis of variables for prediction of mechanical ventilation and in-hospital mortality is shown in Table 1. Variables associated with requirement for mechanical ventilation and early in-hospital mortality were severity of injury, BHT, hemodynamic instability, pulmonary infection during hospital stay, and progressive neurologic deterioration. In addition, the nature of the injury on magnetic resonance imaging and mechanical ventilation were associated with in-hospital mortality. Age, gender, level of injury, type of injury, associated injuries, and timing of surgery had no correlation with requirement for mechanical ventilation or in-hospital mortality. None of the patients had significant surgery-related complications or comorbid disorders. Complications related to DVT could not be commented on because there was no consistency in monitoring; however, there was no record of deaths attributable to pulmonary thromboembolism. ROC analysis revealed that BHT was a good discriminator for ventilation, and the best cutoff obtained was 12 s (Fig. 1). To obtain a dichotomous response for BHT, patients were categorized as above and below the cutoff. The patients with ASIA Impairment Scale Grades A and B were categorized as severe

ROC Curve for BHT and ventilation

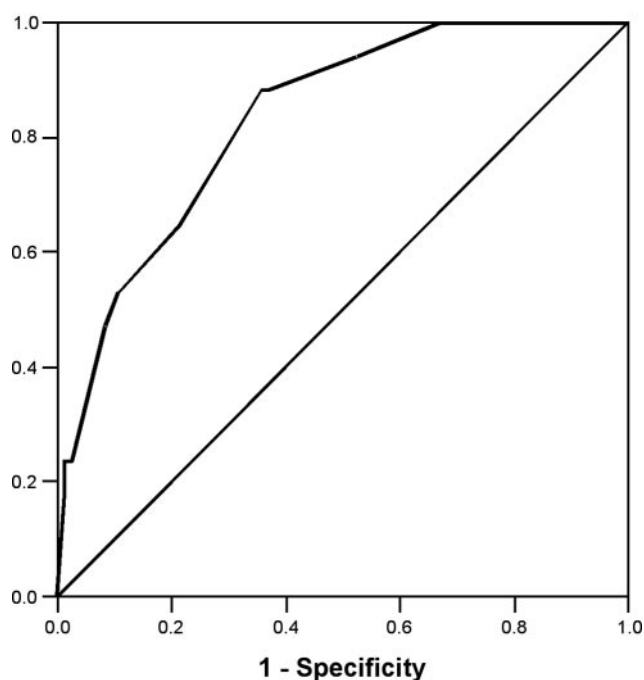


Figure 1. Receiver operating characteristics of breath-holding time (BHT) and need for mechanical ventilation. Area under the curve was 0.83 (95% CI: 0.74–0.93), indicating good discriminatory ability of BHT for ventilation ($P = 0.000$). The best cutoff for BHT for requirement of ventilation was 12 s, with a sensitivity of 0.9 and a 1 – specificity of 0.3.

injury and the remaining patients as absence of severe injury.

Table 2 shows the final model for the independent predictors of ventilation identified on multivariate analysis. The R^2 of the model was 0.734 ($P = 0.000$). The Hosmer-Lemeshow statistic (which tests the null hypothesis that the model fits the data) was not significant ($P = 0.166$). There was no significant correlation between the variables. A predictor score developed using the regression coefficients of these variables is shown in Table 2. The area under the ROC curve for PRIM score for prediction of mechanical ventilation was 0.95 (95% bias-corrected CI: 0.87–1.00), which indicates excellent model discrimination. The best cutoff score for prediction of ventilation was 45 (sensitivity 0.76 and 1 – specificity 0.03). Internal

Table 3. Internal and External Validation of the PRIM Score for Prediction of Mechanical Ventilation in Cervical Spine Injury

| Observed ventilation | Predicted ventilation | | | | | |
|----------------------|-------------------------------|------------|-------|-----------------------------|------------|-------|
| | Development set ($n = 101$) | | | Validation set ($n = 87$) | | |
| | No | Yes | Total | No | Yes | Total |
| No | 81 (80.1%) | 4 (4%) | 85 | 63 (72.4%) | 5 (5.7%) | 68 |
| Yes | 3 (3%) | 13 (12.8%) | 16 | 2 (2.3%) | 17 (19.5%) | 19 |
| Total | 84 | 17 | 101 | 76 | 9 | 87 |

PRIM = Predictors of Respiratory Insufficiency and Mortality.

^a Development set—Good correlation between predicted and observed mechanical ventilation (Spearman correlation 0.74 [$P, 0.000$]), no statistically significant difference between predicted and observed ventilation.

^b Validation set—Spearman correlation 0.78 ($P, 0.000$), no statistically significant difference between predicted and observed outcomes.

cross-validation of the PRIM score for ventilation (Table 3) shows good correlation and no statistically significant difference between predicted and observed outcomes. The odds ratio of mechanical ventilation with predicted ventilation was 87.75 (95% CI: 17.5–437) with a PPV of 81%, an NPV of 95%, and an accuracy of 93% for predicted ventilation.

Table 4 shows the independent predictors of in-hospital mortality identified on multivariate logistic regression analysis. The R^2 of the model was 0.718 ($P = 0.000$). The goodness of fit assessed with the Hosmer-Lemeshow statistic ($P = 0.54$) indicates that the model fits the data well. A predictor score developed based on the regression coefficients of the independent predictor variables is shown in Table 4. The area under the ROC curve for the PRIM score for prediction of in-hospital mortality in CSI was 0.96 (95% bias-corrected CI: 0.92–1.00), which indicates excellent model discrimination of the score. The best cutoff score for prediction of mortality was 50 at a sensitivity of 0.83 and a 1 – specificity of 0.02. There was no statistically significant difference between predicted and observed mortality (Table 5). The predicted outcome using the PRIM score for in-hospital mortality had an odds ratio of 105.3 (95% CI: 18.4–600.7), a PPV of 86.7%, an NPV of 94.2%, and an accuracy of 93.1%.

External Validation of PRIM Scores

The area under the ROC curve for the PRIM score for prediction of mechanical ventilation in the validation set was 0.97 (95% bias-corrected CI: 0.95–1.0) and

Table 2. Development of PRIM Score for Prediction of Mechanical Ventilation in Acute Cervical Spine Injury

| Variables included in model | B | SE | Wald | P | Exp (B) | Score |
|--|------|------|-------|-------|---------|-------|
| Severe injury (ASIA impairment Scales A and B) | 2.10 | 1.08 | 3.80 | 0.051 | 8.16 | 15 |
| Hemodynamic instability | 3.11 | 1.47 | 4.49 | 0.034 | 22.52 | 25 |
| BHT <12 s | 2.80 | 1.20 | 5.46 | 0.020 | 16.48 | 20 |
| Pulmonary infection | 3.66 | 1.15 | 10.14 | 0.001 | 38.85 | 25 |
| Neurological deterioration | 2.18 | 1.10 | 3.91 | 0.048 | 8.87 | 15 |

Wald is the statistic used; the ratio of B to SE , squared, equals the Wald statistic. If the Wald statistic is significant (i.e., $P < 0.05$) then the parameter is useful to the model.

BHT = breath-holding time; ASIA = American Spinal Injury Association; PRIM = predictors of respiratory insufficiency and mortality; B = the beta coefficient for the variable in the model; SE = the standard error for beta.

^a The score of an individual patient is the sum of the scores of the variables present.

^b A total score of 45 and more predicts requirement for mechanical ventilation.

Table 4. Development of PRIM Score for Prediction of In-Hospital Mortality in Cervical Spine Injury

| Variables included in model | B | SE | Wald | P | Exp (B) | Score |
|--|------|-------|------|------|---------|-------|
| Severe injury (ASIA impairment Scales A and B) | 2.69 | 1.345 | 3.99 | 0.05 | 14.74 | 20 |
| Hemodynamic instability | 2.72 | 1.45 | 3.53 | 0.05 | 15.18 | 20 |
| Neurological deterioration | 4.26 | 1.59 | 7.12 | 0.01 | 70.51 | 40 |
| Mechanical ventilation | 2.56 | 0.96 | 7.10 | 0.01 | 12.88 | 20 |

Wald is the statistic used; the ratio of B to se, squared, equals the Wald statistic. If the Wald statistic is significant (i.e., $P < 0.05$) then the parameter is useful to the model.

PRIM = predictors of respiratory insufficiency and mortality; ASIA = American Spinal Injury Association; B = the beta value for the variable in the model; SE = the standard error for beta.

^a The score of an individual patient is the sum of the scores of the variables present.

^b A total score of 50 and more predicts early in-hospital mortality.

Table 5. Internal and External Validation of PRIM Score for Prediction of In-Hospital Mortality in Cervical Spine Injury

| Observed mortality | Predicted mortality | | | | | |
|--------------------|---------------------------|------------|-------|-------------------------|------------|-------|
| | Development set (n = 101) | | | Validation set (n = 87) | | |
| | No | Yes | Total | No | Yes | Total |
| No | 81 (81.2%) | 2 (2%) | 83 | 66 (57.5%) | 6 (5.2%) | 72 |
| Yes | 5 (5.1%) | 13 (13.1%) | 18 | 0 (0%) | 15 (13.1%) | 15 |
| Total | 86 | 15 | 101 | 66 | 18 | 87 |

PRIM = predictors of respiratory insufficiency and mortality.

^a Development set—good correlation between predicted and observed in-hospital mortality (Spearman correlation 0.761 [$P, 0.000$]), no statistically significant difference between predicted and observed ventilation.

^b Validation set—Spearman correlation 0.835 ($P, 0.000$), no statistically significant difference between predicted and observed outcomes.

0.98 (95% bias-corrected CI: 0.97–1.0) for in-hospital mortality, consistent with excellent model discrimination. A good correlation was seen between predicted end points and observed ventilation requirement and in-hospital mortality rates (Tables 3 and 5). The odds ratio for requiring mechanical ventilation in patients with predicted ventilation was 107.1 (95% CI: 19–601.2), and the predicted ventilation using the PRIM score for ventilation had a PPV of 77.3%, an NPV of 96.9%, and an overall accuracy of 91.9%. The PRIM score for in-hospital mortality applied to the validation set had an odds ratio of 165 for in-hospital mortality, a PPV of 71.4%, an NPV of 100%, and an overall accuracy of 93.1%. Surgical stabilization was deferred because of adverse predicted outcome in 16 patients in the validation set. The mortality was 81.3% in these patients. In the operated patients, the mortality was 2.1%, with a PPV of 66% and an NPV of 100%. In nonoperated patients, the PPV was 86.6% and the NPV was 100%.

DISCUSSION

In this study, independent predictors of ventilation and in-hospital mortality in patients with traumatic ACSI were identified, and a simple bedside risk prediction score, the PRIM score, was developed. The score performed well on both internal and external validation.

Recent stabilization techniques and pharmacological advancements have resulted in a substantial reduction of risk of death and major complications for

patients with ACSI. However, the presence of complete injury, respiratory insufficiency, and hemodynamic instability is still associated with an increased risk of mortality, which is inherent in the natural history of the disease itself.^{3,5,6} Thus, precise prediction of individual patient outcome has particular importance during discussions with patients and families regarding prognosis or for clinical decision making.

The mortality rate due to traumatic ACSI observed in the population studied was relatively high compared with mortality rates previously reported in other series,^{6–8} which reflects the high percentage of patients with severe injury (ASIA Impairment Scale Grades A and B) and hemodynamic instability in this series. In agreement with findings from other studies, higher mortality rates were observed in patients who were hemodynamically unstable.^{3,9} Most patients had cervical injury at C4–5, consistent with other studies.^{8,10,11} In contrast to several other studies, level of injury was not an independent variable predicting mechanical ventilation or mortality. CSI is a dynamic process, and the level of cord injury is not restricted to the initial level of injury. Moreover, the severity of injury and the physiological consequences of injury, such as hemodynamic compromise and respiratory compromise resulting from autonomic and motor involvement, determine the outcome. Given the heterogeneous nature of involvement and the dynamic nature of the disease, the aforementioned consequences would determine the outcome rather than the level of injury. A similar observation has been made by Winslow et al.¹² The neurologic deterioration due to secondary injury was an important predictor of mechanical ventilation and mortality, emphasizing the need for early referral to specialized centers and intensive care to initiate measures for reduction of secondary injury. Secondary deterioration occurred in both operated and conservatively managed patients and was not attributable to any specific management event.

Models for prediction of mechanical ventilation in postoperative and intensive care unit settings are usually based on spirometric pulmonary function tests or laboratory values of adequacy of oxygenation (P_{aO_2} , F_{iO_2}/P_{aO_2} , and alveolar-arterial difference in oxygen tension). Patients with ACSI are immobilized in supine position, and their performance of spirometry could be difficult. Early detection of mechanical

respiratory failure that results from motor weakness in these patients is not possible or reliable with the blood gas analysis. Thus, BHT was used as a simple bedside pulmonary function test to assess the adequacy of vital capacity, which is the first to be affected in CSI.^{13,14} Because there were no cutoff values established in the literature for the use of BHT in patients with CSI, ROC analysis was used to determine the best cutoff. BHT had good discriminatory power to identify patients requiring mechanical ventilation (area under ROC curve 0.8, with the best cutoff value at 12 s). The test of BHT requires no equipment, is simple to interpret, understand, and perform, and has good reliability. However, its limitations, including the necessity for the patient to understand and cooperate, and the inability of chest-injured and unconscious patients to perform the test, have to be considered.

The scores were derived for patients who underwent surgical stabilization of the cervical spine in a tertiary referral center, which could have resulted in referral and selection bias. Hemodynamic instability and respiratory infection were higher in the validation set. Overall mortality was comparable between the sets. Validation of PRIM scores on the validation set yielded a lower PPV for both ventilation and mortality than validation on the development set. This could have resulted from patients with higher scores and poor predicted outcome receiving more intensive management. There was a considerable emphasis on early surgical stabilization during the period when the development set of data was collected, which resulted in surgery being performed on patients with suboptimal hemodynamic and respiratory stabilization. Analysis of the development set of data showed no significant difference in neurologic deterioration between patients who underwent early surgery and delayed surgery. Complications such as postoperative hemodynamic instability and respiratory insufficiency were higher with early surgical stabilization (not shown in the results), as observed by authors earlier.^{15,16} During the period of validation of score, surgery was undertaken after hemodynamic and respiratory stabilization. For 16 of the 87 patients in the validation set, surgical stabilization was not performed because of a predicted high risk of mortality, and they were managed conservatively. The mortality in these patients was 81.3%. The operative mortality was 17.8% in the development set compared with 2.3% in the validation set. There were 6.9% of operated patients who required mechanical ventilation compared with 16.8% in the development set. The application of the PRIM scores contributed to effective triaging of patients for surgery and aggressive optimization of identified predictors of mechanical ventilation and mortality.

Limitations

The total sample size was modest ($n = 188$); no formal power calculation was done for this study. The

intent of the study was to use these data to better estimate the primary outcome rates in a representative population of patients. Although there was excellent correlation between observed and predicted need for mechanical ventilation and early in-hospital mortality rates, and validation of the model was performed on the independent data set, additional validation in other subgroups with larger samples might be needed. The independent validation data set was obtained from the same institution that developed the initial model. Validation of the score with data obtained from other institutions is required, because this diversity would lead to stronger external validity. Predictive accuracy is expected to vary with external validation in other multicenter registries. Therefore, one should be cautious when generalizing these findings until the score has been widely tested.

The score includes variables that are amenable to optimization, such as hemodynamic instability and respiratory infection. Another potential concern is incorrect prediction. Because the family of the patient is likely to decide against expensive interventions such as surgery when mortality is forecast, incorrect prediction of survival would result in futile expenditure. However, this tool should not be used to deny care to high-risk patients, but rather to help patients make decisions that are more informed and to reassure low-risk patients that their low-risk estimate is based on a tested mathematical model. This enables family members to realize that aggressive management is likely to result, nonetheless, in an adverse outcome and to accept a decision to reduce or withhold care.

CONCLUSION

PRIM scores were developed based on simple bedside tests (e.g., the BHT) and readily available clinical variables. These are simple to obtain and do not require complex mathematical calculations. Application of these scores results in fairly accurate prediction of a requirement for mechanical ventilation and of in-hospital mortality in patients with ACSI.

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Synthetic Atrial Natriuretic Peptide Improves Systemic and Splanchnic Circulation and Has a Lung-Protective Effect During Endotoxemia in Pigs

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BACKGROUND: Pharmacological blockade of the renin-angiotensin system is thought to maintain gut perfusion during circulatory stress and thereby avoid later failure of distant organs. In this controlled experimental study, we investigated the effects of carperitide, a synthetic atrial natriuretic peptide that inhibits the renin-angiotensin system, on the systemic and splanchnic circulation during fluid-resuscitated endotoxemia in pigs.

METHODS: Sixteen domestic pigs of both sexes were randomly divided into 2 groups. The pigs were anesthetized and their lungs ventilated before receiving either saline (Group A: $n = 8$) or carperitide (Group B: $n = 8$). After a baseline measurement was taken, the pigs from both groups received a continuous infusion ($1.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) of endotoxin for 240 min. Group B received a continuous infusion of carperitide ($0.05 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) starting 30 min before the endotoxin infusion and lasting until the end of the study, whereas Group A received the same volume of saline. Fluid resuscitation was titrated to maintain pulmonary artery wedge pressure between 10 and 12 mm Hg. Systemic and regional hemodynamics, oxygenation variables, and the arterial-to-intestinal Pco_2 gap were measured at baseline and after endotoxin infusion for 240 min. The primary end points were cardiac index, superior mesenteric artery flow index, and Pco_2 gap at the end of this study (T240).

RESULTS: Cardiac index and superior mesenteric artery flow index in Group B were significantly higher than those in Group A at T240 (83 ± 15 vs $135 \pm 23 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P < 0.001$; 2.6 ± 1.4 vs 7.9 ± 4.8 , $P = 0.01$), respectively. Carperitide administration resulted in a significantly better maintenance of intestinal mucosal perfusion assessed by the Pco_2 gap at T240 (33.0 ± 14.5 vs 11.6 ± 10.0 mm Hg, $P = 0.004$). The $\text{PaO}_2/\text{FiO}_2$ ratio in Group B was significantly greater than that in Group A from T60 to T240.

CONCLUSIONS: In this porcine fluid-resuscitated endotoxemia model, a low dose of carperitide administered before endotoxemia maintained systemic and splanchnic circulation, and prevented the deterioration of oxygenation. Atrial natriuretic peptide infusion is a potentially beneficial therapy with respect to systemic and splanchnic circulation as well as the respiratory system during sepsis.

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Sepsis and septic shock are major causes of morbidity and mortality.¹ The gut mucosa has been identified as one of the most important targets of injury during septic shock. The pathophysiology of the hemodynamic derangement is complex and involves both cardiac and peripheral circulation dysfunction.² Fluid resuscitation is important for restoring mean

circulating filling pressure during septic shock.³ However, tissue hypoperfusion often occurs after adequate intravascular volume replacement, necessitating the administration of vasoactive drugs.⁴ To prevent gut ischemia and improve gut perfusion, numerous gut-directed therapeutic approaches have been attempted by administration of these vasoactive drugs.⁵⁻⁷ Although hemodynamics might seem to be corrected, hidden tissue dysoxia may persist. Therefore, the search for drugs that facilitate resuscitation of septic shock remains an important challenge. A new strategy has been proposed for the purpose of recruiting microcirculation by using vasodilators.⁸

The renin-angiotensin system (RAS) is highly active during septic shock and may be involved in the pathophysiology of the markedly deteriorated splanchnic circulation.⁹ It has been suggested that pharmacological blockade of the RAS can maintain gut perfusion during

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circulatory stress and possibly avoid later failure of distant organs. This concept has been evaluated using angiotensin-converting enzyme (ACE) inhibitors¹⁰ and angiotensin receptor blockade (ARB).^{9,11}

Human atrial natriuretic peptide (ANP) is a hormone secreted by distension of the atrial wall. It has been shown that ANP inhibits sympathetic activity.¹² Reports have suggested that carperitide, a synthetic ANP, inhibits the RAS^{13,14} in addition to inducing an antiinflammatory effect.¹⁵

Herein, we discuss the effects of carperitide on the systemic and splanchnic circulation during endotoxemia in pigs.

METHODS

All experimental procedures used in this investigation were reviewed and approved by the Institutional Animal Care Committee of Nagasaki University. Sixteen pigs of both sexes, each weighing 25–35 kg, were used in this study. The pigs were fasted overnight but given free access to water before beginning the experiment.

Anesthesia and Surgical Procedures

Pigs were IM sedated with ketamine hydrochloride, 20 mg/kg. After IV access was established via an ear vein, the pigs were anesthetized with IV α -chloralose, 100 mg/kg, and fentanyl, 10 μ g/kg, followed by continuous infusion of α -chloralose, 10 mg \cdot kg⁻¹ \cdot h⁻¹, and fentanyl, 10 μ g \cdot kg⁻¹ \cdot h⁻¹, throughout the study period. Through a midline cervical incision, the trachea was intubated for connection to a Harvard respiratory pump (Harvard Apparatus, South Natick, MA). Mechanical ventilation was facilitated by intermittent administration of vecuronium, 0.2 mg/kg. The lungs were ventilated with 100% oxygen with a positive end-expiratory pressure of 5 cm H₂O throughout the study period. Tidal volume was maintained at 10 mL/kg, and a minute volume was adjusted to maintain the end-tidal carbon dioxide (ETCO₂) concentration at 35–45 Torr. ETCO₂ was continuously monitored using a gas analyzer (Capnomac Ultima, Datex, Helsinki, Finland). Central venous, arterial, and pulmonary arterial catheters were inserted through the right jugular vein, the right internal carotid artery, and the left jugular vein to administer fluid and drugs, to draw arterial blood samples, and to measure systemic and pulmonary hemodynamics, respectively. After a midline laparotomy was performed, the stomach and the urinary bladder were drained. Ultrasonic flowmetry probes (Transonic Systems, Ithaca, NY) were placed around the superior mesenteric artery (SMA) and the portal vein (PV) to measure SMA and PV flows. The PV was cannulated via a branch of the superior mesenteric vein for infusion of endotoxin and blood sampling.¹⁶ The tonometry catheter (Tonometrics™ catheter, TONO-8F, Datex-Ohmeda, Helsinki, Finland) was

placed in the jejunum to measure the intestinal-to-arterial Pco₂ difference (Pco₂ gap) by tonometer (Tonocap™, Datex-Ohmeda) to assess jejunal perfusion.¹¹ Blood temperature was maintained between 37.5°C and 38.5°C using an electrical heating pad and a heating lamp. All pigs were allowed to stabilize for 1 h after the surgical procedures.

Hemodynamic Measurements and Blood Gas Measurements

For continuous measurements and recordings of heart rate (HR), mean arterial blood pressure (MAP), mean pulmonary arterial blood pressure (MPAP), and central venous pressure (CVP), the arterial and pulmonary artery catheters were connected to pressure transducers, whereas pulmonary artery wedge pressure (PAWP) was recorded intermittently.

At each measurement point, arterial and mixed venous and PV blood samples were drawn from the indwelling catheters and analyzed using a blood gas analyzer (ABL SYSTEM 625, Radiometer, Copenhagen, Denmark) for oxygen pressure (Po₂, Torr), carbon dioxide pressure (Pco₂, Torr), oxygen saturation (So₂, %), base excess (mmol/L), lactate (mmol/L), and total hemoglobin concentration (Hb, g/dL). A ratio of the arterial oxygen pressure (PaO₂) to fraction of inspired oxygen (FIO₂) (P/F ratio) was calculated to assess the level of oxygenation.

Cardiac output was measured by thermodilution (Vigilance CCO Monitor, Edwards Lifesciences, Irvine, CA) and determined as the mean of a triplicate of 3-mL injections of ice-cold saline. Cardiac index (CI, mL \cdot kg⁻¹ \cdot min⁻¹), SMA flow index (SMAI, mL \cdot kg⁻¹ \cdot min⁻¹), and PV flow index (PVI, mL \cdot kg⁻¹ \cdot min⁻¹) were calculated on the basis of body weight. Stroke volume index (mL \cdot kg⁻¹ \cdot beat⁻¹) was calculated as CI/HR. Systemic vascular resistance index (mm Hg \cdot L⁻¹ \cdot kg⁻¹ \cdot min⁻¹) was calculated as (MAP – CVP)/CI, and pulmonary vascular resistance index (PVRI, mm Hg \cdot L⁻¹ \cdot kg⁻¹ \cdot min⁻¹) was calculated as (MPAP – PAWP)/CI.

Systemic oxygen delivery index (Do₂I), systemic oxygen consumption index (Vo₂I), the mesenteric oxygen delivery index (mes-Do₂I), and intrapulmonary shunt were calculated using the following formulas:

$$\text{Do}_2\text{I (mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = \text{CI} \times \text{Cao}_2,$$

where Cao₂ is the arterial oxygen content;

$$\text{Vo}_2\text{I (mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = (\text{CI} \times [\text{Cao}_2 - \text{Cvo}_2]),$$

where Cvo₂ is the mixed venous oxygen content;

$$\text{Mes} - \text{Do}_2\text{I (mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = \text{SMAI} \times \text{Cao}_2$$

Intrapulmonary shunt (%)

$$= (\text{Cc}'\text{o}_2 - \text{Cao}_2) / (\text{Cc}'\text{o}_2 - \text{Cvo}_2),$$

Table 1. Hemodynamic Variables in Control Animals (Group A; $n = 8$) and Carperitide-Treated Animals (Group B; $n = 8$)

| | T0 | T30 | T60 | T90 | T120 | T150 | T180 | T210 | T240 |
|--------------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| HR (bpm) | | | | | | | | | |
| Group A | 79 ± 16 | 110 ± 26* | 110 ± 18* | 110 ± 14* | 115 ± 21* | 121 ± 19* | 126 ± 26* | 128 ± 24* | 124 ± 24* |
| Group B | 83 ± 16 | 96 ± 22 | 103 ± 24 | 110 ± 28 | 106 ± 35 | 109 ± 44 | 107 ± 45 | 104 ± 43 | 101 ± 34 |
| MAP (mm Hg) | | | | | | | | | |
| Group A | 114 ± 11 | 118 ± 14 | 93 ± 21* | 90 ± 24* | 86 ± 25* | 84 ± 27* | 82 ± 26* | 81 ± 28* | 79 ± 32* |
| Group B | 113 ± 19 | 116 ± 25 | 98 ± 21* | 96 ± 23* | 101 ± 29† | 102 ± 24 | 103 ± 21 | 102 ± 21 | 104 ± 19 |
| MPAP (mm Hg) | | | | | | | | | |
| Group A | 21 ± 2 | 47 ± 12* | 32 ± 7* | 31 ± 6* | 37 ± 7* | 38 ± 6* | 40 ± 8* | 40 ± 8* | 41 ± 8* |
| Group B | 20 ± 2 | 29 ± 11*‡ | 28 ± 6* | 26 ± 6† | 30 ± 4*§ | 32 ± 7* | 32 ± 6*§ | 32 ± 6*§ | 32 ± 6*§ |
| PAWP (mm Hg) | | | | | | | | | |
| Group A | 13 ± 1 | 12 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 2 | 11 ± 1 |
| Group B | 13 ± 1 | 12 ± 1 | 11 ± 1 | 11 ± 2 | 12 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 1 |
| CVP (mm Hg) | | | | | | | | | |
| Group A | 8 ± 1 | 9 ± 3 | 8 ± 1 | 8 ± 2 | 8 ± 1 | 8 ± 2 | 9 ± 2 | 8 ± 2 | 9 ± 2 |
| Group B | 8 ± 1 | 8 ± 1 | 8 ± 1 | 7 ± 1 | 8 ± 1 | 8 ± 1 | 8 ± 1 | 7 ± 1 | 8 ± 1 |

Values are mean ± sd.

HR = heart rate; MAP = mean arterial blood pressure; MPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; CVP = central venous pressure.

* $P < 0.01$, † $P < 0.05$ versus the T0 value in the same group; ‡ $P < 0.01$, § $P < 0.05$ versus the value obtained at the same time in Group A.

where $Cc'o_2$ is pulmonary capillary oxygen content = $1.39 \times Hb + 0.0031 \times (713 - PaCO_2/0.8)$;

$$\text{Oxygen content (mL O}_2\text{/100 mL blood)} = 1.39 \times Hb \times So_2 + 0.0031 \times Po_2$$

where Po_2 is the partial pressure of oxygen and So_2 is oxygen saturation.

Experimental Design

Pigs were randomly divided into 2 groups to receive either saline (Group A; $n = 8$) or carperitide (Group B; $n = 8$). After a baseline measurement was taken (T0), the pigs received a continuous infusion ($1.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) of endotoxin via the PV¹⁷ for 240 min. Group B received a continuous infusion of carperitide ($0.05 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) starting 30 min before the endotoxin infusion and lasting until the end of the study, whereas Group A received the same volume of saline. Normovolemia was maintained with a continuous infusion ($20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) of lactated Ringer's solution containing dextran 40. The infusion was intended to maintain the PAWP between 10 and 12 mm Hg. If, however, continuous infusion was insufficient to maintain the PAWP, 50 mL of the same solution was repeatedly injected. CI, P/F ratio, Do_2I , Vo_2I , mes- Do_2I , and Pco_2 gap were measured at 0, 60, 120, 180, and 240 min after starting the endotoxin infusion (expressed as T0, T60, T120, T180, and T240), and all other variables were measured every 30 min.

Endotoxin

Lipopolysaccharide (LPS) from *Escherichia coli*, serotype 0127:B8 (Sigma-Aldrich, St. Louis, MO), was dissolved in saline.

Statistical Analysis

All data are presented as mean ± sd. Differences within groups were analyzed with a repeated-measures analysis of variance and Student-Newman-Keuls multiple comparisons test to compare each time point with baseline (T0). Differences between Group A and Group B were analyzed using the 2-tailed unpaired *t*-test. Differences with *P* values <0.05 were considered statistically significant.

RESULTS

There were no significant differences in weight or sex between the 2 test groups. Changes in hemodynamic variables are shown in Table 1. There were no significant differences in any systemic or pulmonary hemodynamics at baseline (T0). In Group A, MAP decreased and HR and MPAP increased after endotoxin infusion. By contrast, MAP and HR in Group B were stable during the study period. MPAP increased significantly compared with the T0 value for both groups, but the increase in MPAP for Group B was less than that for Group A. Both PAWP and CVP remained unchanged, and there was no significant difference between the 2 groups.

Changes in hemodynamic and oxygen transport variables are shown in Table 2. CI in Group B was significantly greater than that in Group A at T180 and T240 (112 ± 27 vs $153 \pm 42 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P = 0.034$; 83 ± 15 vs 135 ± 23 , $P < 0.001$, respectively). In addition, stroke volume index in Group A decreased earlier and was significantly lower than that in Group B at T180 and T240 (1.0 ± 0.3 vs $1.4 \pm 0.3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P = 0.018$; 0.7 ± 0.2 vs 1.3 ± 0.2 , $P < 0.001$, respectively). PVRI increased significantly after endotoxin infusion in both groups, but PVRI in Group A was higher than that in Group B. Do_2I and Vo_2I in Group B remained unchanged, whereas Do_2I in Group

Table 2. Hemodynamic and Oxygen Transport Variables in Control Animals (Group A; $n = 8$) and Carperitide-Treated Animals (Group B; $n = 8$)

| | T0 | T60 | T120 | T180 | T240 |
|---|------------|------------|------------|-------------|-------------|
| CI ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) | | | | | |
| Group A | 144 ± 24 | 168 ± 25 | 149 ± 28 | 112 ± 27* | 83 ± 15† |
| Group B | 162 ± 38 | 186 ± 34 | 171 ± 42 | 153 ± 42‡ | 135 ± 23§ |
| SVI ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{beat}^{-1}$) | | | | | |
| Group A | 1.9 ± 0.4 | 1.6 ± 0.4 | 1.4 ± 0.4† | 1.0 ± 0.3† | 0.7 ± 0.2† |
| Group B | 2.0 ± 0.3 | 2.0 ± 0.4 | 1.7 ± 0.2 | 1.4 ± 0.3†‡ | 1.3 ± 0.2†§ |
| SVRI ($\text{mm Hg}^{-1} \cdot \text{L}^{-1} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) | | | | | |
| Group A | 755 ± 128 | 522 ± 170 | 533 ± 155 | 696 ± 316 | 851 ± 327 |
| Group B | 688 ± 248 | 510 ± 180* | 591 ± 265 | 675 ± 279 | 739 ± 232 |
| PVRI ($\text{mm Hg}^{-1} \cdot \text{L}^{-1} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) | | | | | |
| Group A | 67 ± 30 | 224 ± 80† | 151 ± 42† | 199 ± 49† | 341 ± 123† |
| Group B | 47 ± 18 | 92 ± 61*§ | 101 ± 52 | 99 ± 47*§ | 138 ± 36†§ |
| Do ₂ I ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) | | | | | |
| Group A | 18.0 ± 3.5 | 22.1 ± 3.3 | 20.8 ± 5.2 | 14.3 ± 6.7 | 10.0 ± 4.2† |
| Group B | 18.8 ± 4.6 | 22.1 ± 3.6 | 20.9 ± 5.2 | 18.5 ± 4.1 | 16.0 ± 1.4§ |
| Vo ₂ I ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) | | | | | |
| Group A | 4.6 ± 1.6 | 5.2 ± 2.8 | 5.0 ± 1.7 | 4.6 ± 1.9 | 4.1 ± 1.8 |
| Group B | 3.7 ± 1.1 | 3.9 ± 1.0 | 4.6 ± 2.6 | 5.4 ± 3.4 | 4.7 ± 1.6 |

Values are mean ± sd.

CI = cardiac index; SVI = stroke volume index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; Do₂I = systemic oxygen delivery index; Vo₂I = systemic oxygen consumption index.

* $P < 0.05$, † $P < 0.01$ versus the T0 value in the same group; ‡ $P < 0.05$, § $P < 0.01$ versus the value obtained at the same time in Group A.

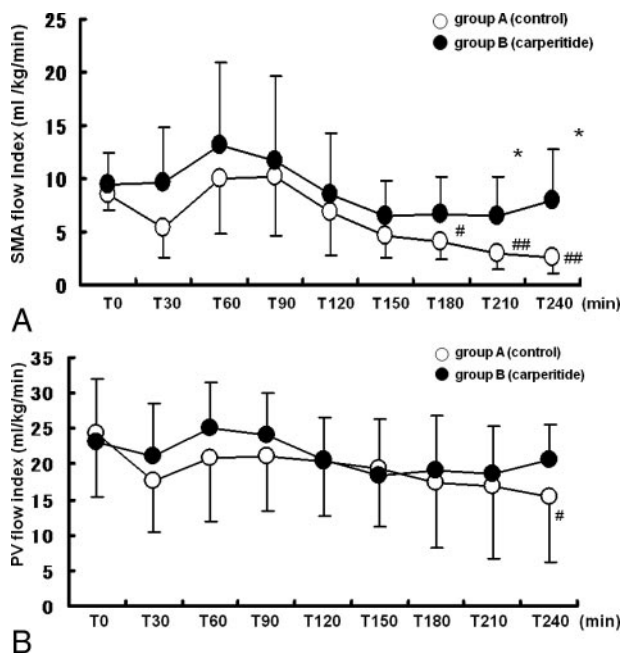


Figure 1. Changes in superior mesenteric artery (SMA) flow index and portal vein (PV) flow index in both groups. Data are shown as mean ± sd. * $P < 0.05$ versus the value obtained at the same time in Group A. ## $P < 0.01$, # $P < 0.05$ versus the T0 value in the same group.

A decreased significantly at T240 (10.0 ± 4.2 vs $16.0 \pm 1.4 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P = 0.002$).

In Group A, SMAI decreased in the late phase. However, in Group B, SMAI remained unchanged and was significantly greater than that in Group A at T210 and T240 (3.0 ± 1.6 vs $6.5 \pm 3.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P = 0.025$; 2.6 ± 1.4 vs 7.9 ± 4.8 , $P = 0.01$, respectively) (Fig. 1). PVI in Group A decreased significantly at T240 compared with T0, but there were no significant

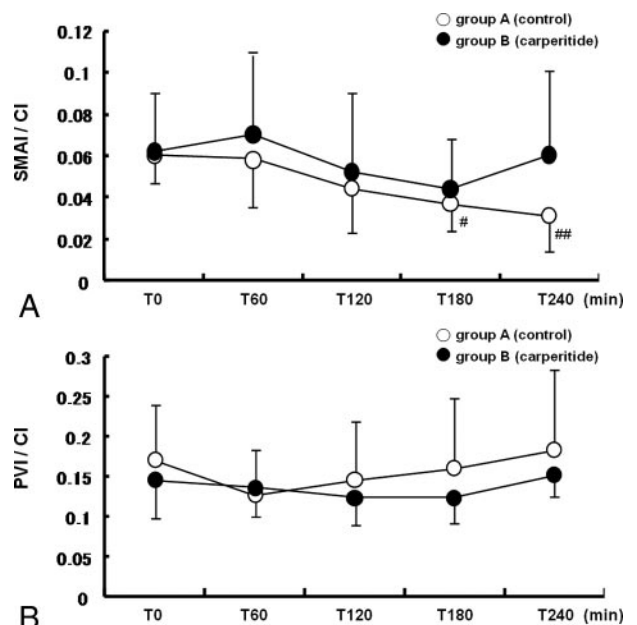


Figure 2. Changes in superior mesenteric artery flow index (SMAI)/cardiac index (CI) and portal vein flow index (PVI)/CI in both groups. Data are shown as mean ± sd. ## $P < 0.01$, # $P < 0.05$ versus the T0 value in the same group.

differences between the 2 groups (Fig. 1). There was no significant difference in SMAI/CI and PVI/CI between the 2 groups (Fig. 2). Mes-Do₂I remained unchanged in Group B but decreased significantly in Group A from T180 to T240. Thus, there was a significant difference in the mes-Do₂I between the 2 groups at T240 (0.3 ± 0.2 vs $1.0 \pm 0.7 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P = 0.028$) (Fig. 3). The Pco₂ gap in Group A increased significantly after endotoxin infusion. During the same period, the Pco₂ gap in Group B remained unchanged and was significantly lower

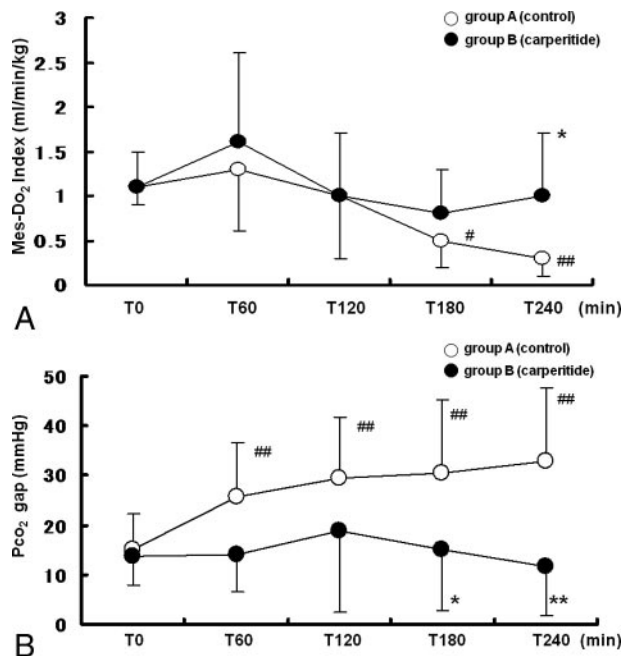


Figure 3. Changes in mesenteric oxygen delivery (mes-Do₂) index and intestinal-to-arterial P_{CO₂} difference (P_{CO₂} gap) in both groups. Data are shown as mean ± SD. ***P* < 0.01, **P* < 0.05 versus value obtained at the same time in Group A. ###*P* < 0.01, #*P* < 0.05 versus the T0 value in the same group.

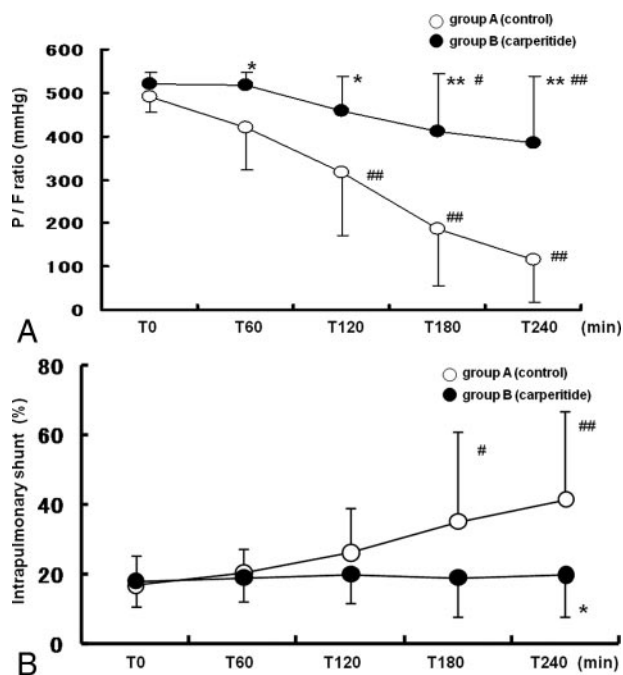


Figure 4. Changes in the ratio of arterial oxygen pressure to fraction of inspired oxygen (P_{aO₂}/F_IO₂) and intrapulmonary shunt in both groups. Data are shown as mean ± SD. ***P* < 0.01, **P* < 0.05 versus the value obtained at the same time in Group A. ###*P* < 0.01, #*P* < 0.05 versus the T0 value in the same group.

than that in Group A at T180 and T240 (30.8 ± 14.5 vs 15.1 ± 12.4 mm Hg, *P* = 0.036; 33.0 ± 14.5 vs 11.6 ± 10.0, *P* = 0.004, respectively) (Fig. 3). The P/F ratio decreased significantly after endotoxin infusion in both groups, but the P/F ratio in Group B was

significantly greater than that in Group A at T60, T120, T180, and T240 (Fig. 4). Intrapulmonary shunt in Group B was significantly lower than in Group A at T240 (41.3% ± 25.4% vs 19.5% ± 11.6%, *P* = 0.044) (Fig. 4).

P_{aCO₂} significantly increased in Group A and to a lesser extent in Group B (Table 3). Base excess decreased and lactate increased slightly in Group A, but there was no significant difference between the 2 groups (Table 3). Hb in Group B remained unchanged. However, despite fluid resuscitation, hemoconcentration occurred in Group A (Table 3).

DISCUSSION

We examined the effect of carperitide on systemic and intestinal circulation in an endotoxemia model in which intravascular volume and blood oxygen levels were maintained. We used continuous endotoxin infusion followed by fluid resuscitation to produce a normodynamic shock pattern, with preserved cardiac output and MAP. Therefore, endotoxin infusion resulted in a relatively modest decreasing of arterial blood pressure, slow progression of metabolic acidosis, and low elevation of lactate. Mechanical ventilation using 100% oxygen was applied because of the difficulty in maintaining an optimal oxygen level throughout the study, and to minimize the effect on oxygen delivery.

The RAS is a major contributor to the vasoconstrictive response seen in circulatory stress conditions such as shock states and hypovolemia.^{18–20} Consequently, pharmacological blockade of the RAS has been proposed as a means of maintaining gut perfusion during circulatory stress and thereby possibly avoiding subsequent failure of distant organs. ACE inhibitors²¹ and ARB^{22,23} in animal models have been shown to improve splanchnic perfusion during hypovolemic shock. In an endotoxin shock model, an ACE inhibitor prevented endothelial dysfunction,¹⁰ and ARB increased gut oxygen delivery.^{9,11}

In our study, carperitide, which inhibits RAS, maintained splanchnic circulation and intestinal mucosal perfusion (assessed by the P_{CO₂} gap). The P_{CO₂} gap was used as an indicator of intestinal mucosal blood flow in this study. Some reports showed that hypoperfusion is a key factor in the development of venous and tissue hypercarbia, and, in this way, an increase in blood flow was shown to prevent intramucosal acidosis in sheep endotoxemia.²⁴ In addition, an association between increased P_{CO₂} gap and diminished villi microcirculation in endotoxemic pigs was shown.²⁵ The findings of this study reinforce the idea that the P_{CO₂} gap is mainly dependent on perfusion. By maintaining systemic blood flow and/or by a direct local vasodilatory effect, carperitide may reduce the increase in P_{CO₂} gap. The remarkable ability of carperitide to improve the intestinal P_{CO₂} gap strongly suggests a redistribution of microcirculatory flow. Thus, carperitide

Table 3. PaCO₂, Base Excess, Lactate and Total Hemoglobin Concentration in Control Animals (Group A; n = 8) and Carperitide-Treated Animals (Group B; n = 8)

| | T0 | T60 | T120 | T180 | T240 |
|---------------------------|------------|--------------|--------------|--------------|--------------|
| PaCO ₂ (mm Hg) | | | | | |
| Group A | 35.9 ± 3.2 | 45.2 ± 5.2* | 51.6 ± 8.9† | 59.3 ± 11.4† | 64.0 ± 18.0† |
| Group B | 33.3 ± 1.8 | 38.2 ± 5.1*‡ | 42.4 ± 5.2†‡ | 44.3 ± 7.3‡§ | 48.1 ± 9.7†‡ |
| BE (mmol/L) | | | | | |
| Group A | 5.1 ± 1.8 | 3.3 ± 2.3 | 1.9 ± 2.3 | 0.3 ± 3.6 | -2.3 ± 7.7 |
| Group B | 5.5 ± 2.1 | 4.3 ± 1.3 | 3.1 ± 2.0 | 3.0 ± 2.8 | 3.4 ± 3.7 |
| Lactate (mmol/L) | | | | | |
| Group A | 1.8 ± 0.9 | 2.0 ± 0.9 | 2.5 ± 1.0 | 2.6 ± 1.1 | 3.6 ± 3.2 |
| Group B | 2.1 ± 0.8 | 2.1 ± 0.5 | 2.4 ± 0.5 | 2.5 ± 0.4 | 2.2 ± 0.3 |
| Hb (g/dL) | | | | | |
| Group A | 7.9 ± 1.6 | 8.7 ± 1.9 | 9.4 ± 1.2 | 9.9 ± 1.2 | 10.3 ± 1.5* |
| Group B | 7.1 ± 1.2 | 7.5 ± 1.2 | 7.8 ± 1.0‡ | 7.9 ± 0.7§ | 7.8 ± 1.0§ |

Values are mean ± sd.

Hb = total hemoglobin concentration; BE = base excess.

* $P < 0.05$, † $P < 0.01$ versus the T0 value in the same group; ‡ $P < 0.05$, § $P < 0.01$ versus the value obtained at the same time in Group A.

seems to exert a protective effect against gut mucosal damage.

In this study, maintenance of arterial oxygenation was significantly better in the group receiving carperitide infusion than in the control group. It has been shown that ANP improves pulmonary gas exchange in patients with acute lung injury²⁶ and in a canine model of oleic acid-induced pulmonary edema.²⁷ In the latter study, ANP reduced extravascular lung water, possibly by decreasing vascular permeability and pulmonary vasodilation, and improved pulmonary gas exchange. Endotoxins cause lung injury, which can severely compromise gas exchange and result in pulmonary hypertension.²⁸ In this study, MPAP was decreased in animals receiving carperitide compared with the control group. Therefore, carperitide may help protect the lungs during endotoxin-induced acute lung injury.

It was reported that carperitide induces an anti-inflammatory effect. Carperitide "pretreatment" prevented an increase of serum tumor necrosis factor (TNF)- α levels and reduced the mortality in LPS-challenged mice.¹⁵ TNF- α activates inflammatory cascades, leading to vascular instability and microvascular occlusion that might contribute to septic multiple organ failure.²⁹ ANP biology is not restricted to cardiovascular functions but is linked to the immune system. Although the antiinflammatory effect of carperitide was not investigated in our study, we believe that this could have a significant influence on the circulation and respiratory system. Transcriptional activation of nuclear factor- κ B in LPS-challenged individuals results in a rapid release of TNF- α into the circulatory system. Although a reduction in TNF- α plasma levels leads to improved survival in murine LPS-induced shock,³⁰ anti-TNF- α strategies failed to prevent death in septic patients.³¹ Indeed, anti-TNF- α therapy requires a prophylactic treatment to prevent the deleterious secondary inflammatory responses.¹⁵

This study has some limitations. A comparison of the total volume of infusion between both groups was

not performed in this study. The changes of Hb as an indicator of blood dilution are presented. The hemoconcentration was observed in the control group but not in the carperitide group. It is possible that the volume of infusion decreased due to increase of PAWP as a result of left ventricular failure caused by endotoxin³² and/or plasma extravasation caused by vascular hyperpermeability. However, the reasons for the variation in the volume of infusion have not been fully determined. Although carperitide has a diuretic effect, the urine volume was not measured. In this model, the effects of carperitide on the total volume of infusion and urine volume need to be investigated in future studies.

In addition, we did not examine whether carperitide elicits the same effect when given simultaneously or even after endotoxin application. Moreover, we did not investigate the mechanism by which carperitide has a useful effect on systemic and splanchnic circulation and the respiratory system. Therefore, we cannot comment on the role of this drug for intervention in human sepsis and septic shock patients. Nevertheless, we believe that carperitide may have therapeutic potential for the treatment of early sepsis before the onset of severe sepsis and septic shock.

In conclusion, a low dose of carperitide administered before inducing endotoxemia maintained systemic and splanchnic circulation and prevented the deterioration of oxygenation. ANP infusion could have therapeutic utility with respect to systemic and splanchnic circulation as well as the respiratory system during sepsis.

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Gestation-Related Reduction in Lumbar Cerebrospinal Fluid Volume and Dural Sac Surface Area

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BACKGROUND: Facilitation of the spread of neuraxial anesthesia in pregnant women may be attributable in part to compression of the dural sac by the engorged epidural venous plexus. In this study, we used magnetic resonance imaging to examine pregnancy-induced changes in the lumbosacral cerebrospinal fluid (CSF) volume and dural sac surface area.

METHODS: Magnetic resonance images of 18 healthy women (mean age 29 yr, mean height 158 cm, and mean weight 58 kg) were obtained to measure lumbosacral CSF volume and dural sac surface area in the nonpregnant and pregnant states (median 36 wk gestation [31–39]) and the paired images were compared.

RESULTS: The mean lumbosacral CSF volume and dural sac surface area in the nonpregnant state were 39.6 ± 5.8 mL and 11.0 ± 0.8 cm², respectively. Pregnancy was associated with compression of the dural sac, resulting in a significantly reduced mean CSF volume (33.2 ± 6.2 mL) and dural sac surface area (9.9 ± 1.0 cm²) in all subjects ($P < 0.001$). The mean change in CSF volume and dural sac surface area was $16.7\% \pm 0.8\%$ and $10.0\% \pm 0.5\%$, respectively. Gestational week (between 31 and 39 wk) correlated significantly with the reduction in CSF volume ($\rho = 0.74$, $P < 0.001$) and dural sac surface area ($\rho = 0.66$, $P < 0.01$).

CONCLUSIONS: These findings indicate an association between gestational week (Weeks 31–39) and a reduction in both CSF volume and dural sac surface area. These reductions may, at least in part, explain the facilitation of the spread of intrathecal anesthesia in pregnant women.

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Pregnancy is associated with a facilitated spread of spinal and epidural anesthesia.^{1–5} Although the mechanism of this phenomenon is not fully understood, compression of the dural sac by the engorged epidural venous plexus is considered to be a factor.^{1–8} Previous magnetic resonance imaging (MRI) studies demonstrated that the compression of the dural sac is associated with the engorged epidural venous plexus in pregnant women.^{7,8} The extent of the reduction in the cerebrospinal fluid (CSF) volume and dural sac surface area induced by dural sac compression, however, is unclear. Lumbosacral CSF volume and dural sac surface area are major determinants of the sensory block spread of spinal and epidural anesthesia, respectively.^{9–12} We previously reported a significant correlation between the maximum cephalad extent of sensory blockade level of neuraxial anesthesia and the lumbosacral CSF volume or

dural sac surface area based on MRI findings.^{10–12} The purposes of this study were to investigate 1) the extent of the reduction in lumbosacral CSF volume and dural sac surface area induced by dural sac compression, and 2) the relation between gestational week and the reduction in CSF volume and dural sac surface area.

METHODS

The study was conducted at the Tokyo Women's Medical University Hospital in Tokyo, Japan, and was approved by the Hospital Ethics Committee. Eighteen healthy women who provided written informed consent were enrolled in the study. Subjects were eligible for the study if they were 20–40 yr of age and had no obvious spinal postural abnormalities (kyphosis). MRI examinations were performed twice for each subject while they were in a supine position without uterine tilting: in the nonpregnant state (4 women before pregnancy and 14 women 3–7 mo after parturition) and in the pregnant state at gestational Weeks 31–39. The nonpregnant state was confirmed by a negative result on pregnancy testing and a report of menstruation in the previous 4 wk, whereas the pregnant state was confirmed by a positive result on pregnancy testing, ultrasonic confirmation of pregnancy, and a report of last menstruation. An MRI scan was performed when convenient for the subjects and when the MRI facilities were available.

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Low thoracic and lumbosacral axial MRI scans for the measurement of CSF volume and dural sac surface area were obtained using an MRI system (Magnetom Vision, Siemens, Tokyo, Japan) operating at 1.5 T. Axial MRI scans were obtained at 8-mm increments (3 mm thick, 5-mm interval) with a fast-spin echo sequence using a method similar to that previously described.⁹⁻¹² One of the authors (TM) traced the dural margin and spinal cord for each axial MRI scan using the public domain Image J 1.37 program (developed at the Research Services Branch of the National Institutes of Mental Health, Bethesda, MD, and available at <http://rsb.info.nih.gov/ij/>). No attempt was made to trace nerve roots. During quantification, the images were encoded and randomized to blind the investigator to the source of the image with regard to the presence or absence of pregnancy. The center level of the disk between the 11th and 12th thoracic vertebrae was determined, and the axial section area (the area of the dural sac minus spinal cord) and perimeter of the dural sac were measured for images caudal to this site. The axial section area and perimeter were each multiplied by the interval between slices (8 mm) to calculate CSF volume and the dural sac surface area, respectively. Although this calculated volume included the spinal nerve roots, it is hereafter referred to as the CSF volume.

Individual CSF volume and dural sac surface area were compared between the nonpregnant and pregnant states. Furthermore, to investigate where the largest reduction occurred in the spinal canal, an axial section area at each disk level from T11-12 to L5-S1 in the nonpregnant state was compared with that in the pregnant state. Because axial images in different subjects are not necessarily at the same level, 7 axial disk levels were selected as a reference for anatomic segmentation.

Sample size was determined to accomplish the second purpose of the study; that is, to determine the relation between gestational week and the reduction in CSF volume and dural sac surface area. Sample analysis ($\alpha = 0.05$ and $\beta = 0.20$) indicated that 17 subjects were needed to demonstrate a significant correlation coefficient, assuming that the 2 variables were continuous data, and the correlation coefficient between gestational week and the reduction in CSF volume was 0.65, which was based on data from a preliminary study. Continuous data are expressed as mean \pm SD, and discrete data are expressed as medians with ranges. The difference in change between the nonpregnant and pregnant axial section area at the disk level from T11-12 to L5-S1 was analyzed using 1-way analysis of variance followed by *post hoc* Tukey-Kramer multiple comparisons test. Comparisons of MRI measurements between the nonpregnant and the pregnant states were made using the paired *t*-test. Statistical correlation coefficients (ρ) between gestational week and the reduction in CSF volume and dural sac surface area were assessed by Spearman's

Table 1. Patient Characteristics and Magnetic Resonance Imaging Measurements in the Nonpregnant and Pregnant State

| | Nonpregnant | Pregnant |
|---|----------------|-----------------|
| Age (yr) | 29 \pm 4 | — |
| Height (cm) | 158 \pm 4 | — |
| Weight (kg) | 51 \pm 4 | 58 \pm 6* |
| Gestational age (wk) | — | 36 (31-39) |
| Cerebrospinal fluid volume (mL) | 39.6 \pm 5.8 | 33.2 \pm 6.2* |
| Dural sac surface area (cm ²) | 11.0 \pm 0.8 | 9.9 \pm 1.0* |

Values are mean \pm SD or median (range).

* $P < 0.001$ compared with each value in the nonpregnant state.

rank correlation. A P value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics and MRI measurements are presented in Table 1. Figure 1 shows examples of axial MRI scans at the level of the disk, pedicles, and lamina in the nonpregnant and pregnant state, respectively. Comparison of the difference in axial section areas at the 7 disk levels between the nonpregnant and pregnant states among the 7 disk levels demonstrated a significantly larger reduction in the axial section area at the L5-S1 disk level than at T11-12 and at T12-L1 disk levels ($P < 0.01$; Table 2). The difference in the reduction of the axial section area between the T11-12 and L4-5 disk levels was also significant ($P < 0.05$).

Individual lumbosacral CSF volume and dural sac surface area decreased in all subjects in the pregnant state. Mean lumbosacral CSF volume and dural sac surface area in the pregnant state were significantly less than that in the nonpregnant state (Table 1 and Fig. 2; $P < 0.001$). The mean reduction in CSF volume and dural sac surface area was 6.4 ± 2.7 mL and 1.1 ± 0.6 cm², respectively. The corresponding reduction in percent change in CSF volume and dural sac surface area was $16.7\% \pm 0.8\%$ and $10.0\% \pm 0.5\%$, respectively. There were significant correlations between gestational week (Weeks 31-39) and the reduction in CSF volume and dural sac surface area (Fig. 3; CSF volume, $\rho = 0.74$, $P < 0.001$ and dural sac surface area, $\rho = 0.66$, $P < 0.01$).

DISCUSSION

The main finding of this study was that compression of the dural sac was associated with the engorged veins in the epidural space, resulting in a gestation-related reduction in CSF volume and dural sac surface area, although this finding was limited to the third trimester of gestation. Pregnancy-induced compression of the subarachnoid space was reported previously,^{7,8} but the number of subjects examined in these studies was small ($n = 3$, each), and the changes in CSF volume and dural sac surface area induced by pregnancy were not examined. We measured the reduction in CSF volume and dural sac surface area in

Nonpregnant

Pregnant

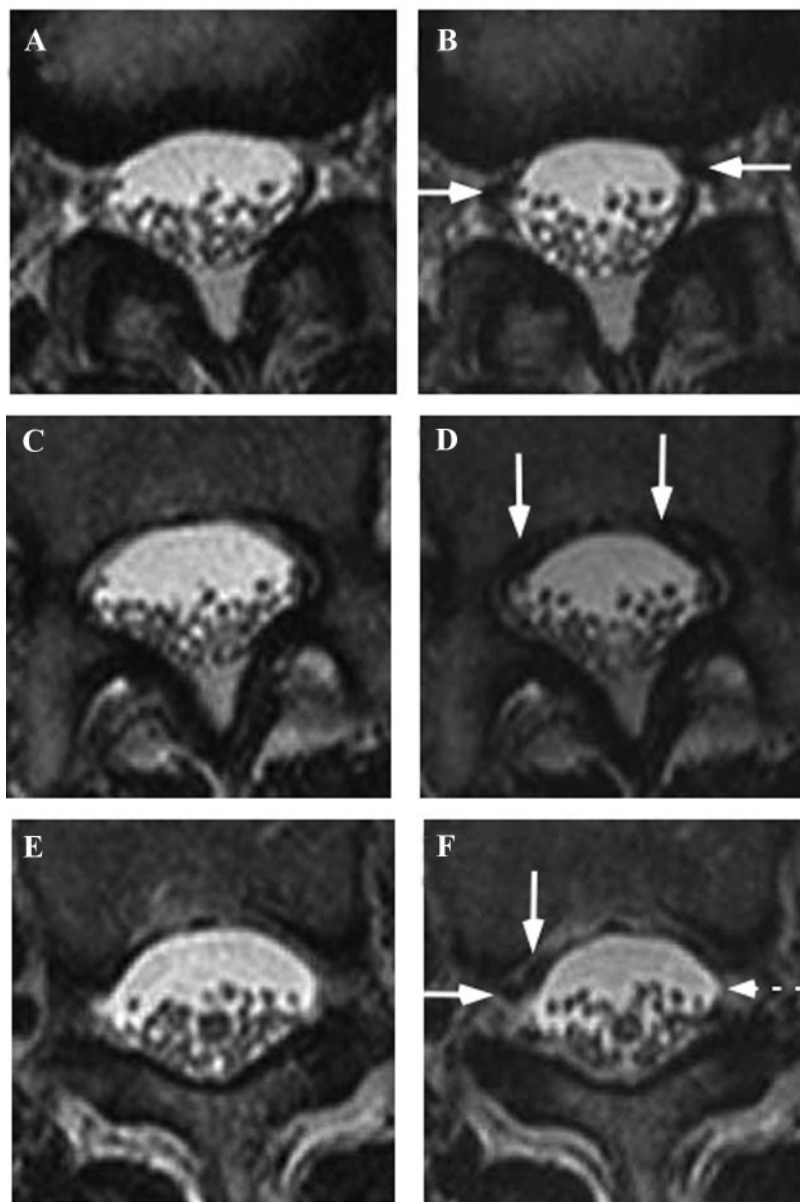


Figure 1. A–F, Magnetic resonance imaging (MRI) scans in the nonpregnant state (left; A, C, and E) and 34 wk gestation (right; B, D, and F) in a 28-yr-old woman whose cerebrospinal fluid (CSF) volume and dural sac surface area decreased from 31.0 to 27.3 mL and 9.4 to 8.7 cm², respectively. In these axial images, anterior is at the top of the figure and anatomic right is at the left of the figure. A, Axial MRI scan at the L1-2 intervertebral disk level in the nonpregnant state. The axial section area at this level was 2.1 cm². B, At 34 wk gestation, the engorged veins (arrows) in the bilateral epidural space are associated with dislocation of the dural sac inward with compression. The axial section area at this level decreased to 1.8 cm². C, Axial MRI scan at the level of the pedicles of L2 in the nonpregnant state. The axial section area at this level was 2.2 cm². D, At 34 wk gestation, the engorged veins (arrows) in the anterior vertebral epidural space are associated with dislocation of the dural sac posteriorly with compression. The axial section area at this level decreased to 1.9 cm². E, Axial MRI scan at the level of the lamina of L1 in the nonpregnant state. The axial section area at this level was 2.2 cm². F, The engorged anterior internal vertebral veins (arrows) are associated with dislocation of the dural sac inward and posteriorly with compression. Note that the dural sac dislocated inward without engorged veins (dashed arrow). The axial section area at this level decreased to 2.0 cm².

Table 2. The Reduction in Axial Section Area at the Disk Level from T11-T12 to L5-S1 Between the Nonpregnant State and in the Pregnant State

| | T11-T12 | T12-L1 | L1-L2 | L2-L3 | L3-L4 | L4-L5 | L5-S1 |
|--|-------------|-------------|-------------|-------------|-------------|--------------|---------------|
| Reduction in axial section area (cm ²) | 0.06 ± 0.20 | 0.16 ± 0.15 | 0.26 ± 0.15 | 0.24 ± 0.19 | 0.25 ± 0.34 | 0.37 ± 0.25* | 0.43 ± 0.39†‡ |

Values are mean ± sd.

* $P < 0.05$ compared with the value at the T11-T12 disc level.

† $P < 0.01$ compared with the value at the T11-T12 disc level.

‡ $P < 0.01$ compared with the value at the T12-L1 disc level.

18 pregnant women to investigate whether the reduction in CSF volume and dural sac surface area is substantial enough to explain, at least in part, the enhanced spread of spinal and epidural anesthesia in pregnant women, because lumbosacral CSF volume and dural sac surface area are major determinants of

the sensory block spread of spinal and epidural anesthesia, respectively.⁹⁻¹²

Based on the MRI findings in this study, it is tempting to conclude that the engorgement of epidural veins is the direct cause of the compression of dural sac because the engorged epidural veins were

Figure 2. Changes in cerebrospinal fluid (CSF) volume and dural sac surface area in the nonpregnant and pregnant states. Individual (filled circles) and mean \pm SD values (open circles) are shown. CSF volumes and dural sac surface area of all subjects were decreased in all subjects during pregnancy. * $P < 0.001$ compared with each value in the nonpregnant state.

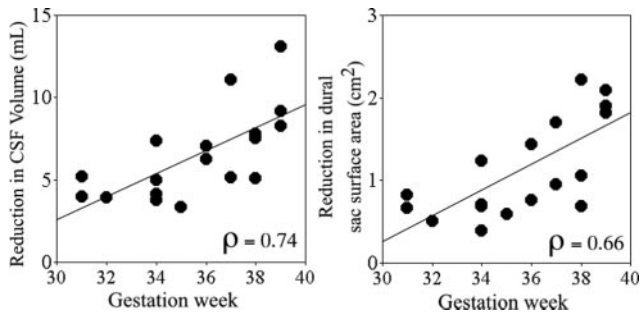
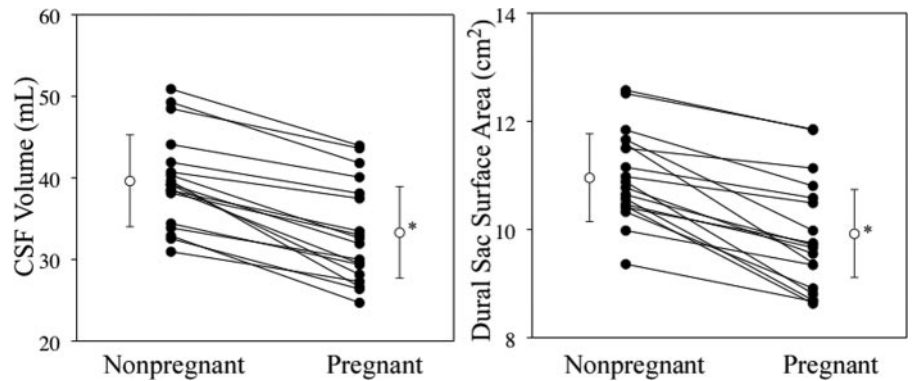


Figure 3. Correlation between gestational week and the reduction in cerebrospinal (CSF) volume (left; $\rho = 0.74$, $P < 0.001$) and between gestational week and the reduction in dural sac surface area (right; $\rho = 0.66$, $P < 0.01$). Although correlation coefficients (ρ) and P values were calculated using Spearman's rank correlation, linear regression lines are presented.

adjacent to the compressed dural sac, but the cause and effect must be interpreted cautiously. Careful examination of some axial images in the pregnant state revealed that the engorged veins are only in contact at limited points along the dural sac and do not broadly compress the dura; rather, fat tissue surrounds the veins and abuts much of the lateral aspect of the dura at the level of the intervertebral foramina. These findings of the effect of pregnancy on dural sac characteristics are similar to those obtained in the study by Hogan et al.,¹³ who investigated the effect of abdominal compression and the mechanics of obesity on dural compression, and reported that the mechanism by which abdominal compression decreases the dural area is probably the inward movement of soft tissue in the intervertebral foramina, which compresses the dural sac. Consequently, inward pressure from the increased pressure in the retroperitoneal area, which is conveyed to the flexible tissue of the intervertebral foramina and hence pushes against the lateral aspect of the dura, may contribute to bilateral dural compression. Furthermore, even if the engorged veins are in the anterior epidural space, which is a closed compartment, the veins are not rigid and therefore it is unlikely that the engorged veins displaced the dural sac without decreasing its volume unless the surrounding compressive force was also increased. Venous intravascular volume, however, was not measured in this study, thus this

study provides no evidence that the engorgement of epidural veins is the direct cause of the compression of dural sac. Further study is required to resolve the mechanism of dural compression.

Hogan et al.¹³ reported that the lumbosacral CSF volume of obese subjects (mean 42.9 mL) is significantly less than that of nonobese subjects (mean 53.5 mL). They also reported that abdominal compression decreases CSF volume by a mean of 3.6 mL. Lee et al.¹⁴ reported that hyperventilation, abdominal compression, and hyperventilation with abdominal compression cause enlargement of the epidural venous plexus, decreasing CSF volume by 3.7, 10.1, and 14.9 mL, respectively. Higuchi et al.¹⁵ reported that lumbar epidural saline injection (5, 10, and 15 mL) compressed the dural sac, resulting in a mean decrease in CSF volume of 2.0 mL in the 5-mL group, 4.4 mL in the 10-mL group, and 7.2 mL in the 15-mL group. The extent of the CSF volume reduction in these 3 studies was comparable to that in this study, although there were differences in the patterns of dural sac compression among these studies.

Previous studies indicated a significant correlation between the lumbosacral CSF volume and the sensory block spread of spinal anesthesia and between the lumbosacral dural sac surface area and sensory block spread of epidural anesthesia.⁹⁻¹² Calculation of the slopes of linear regression in the correlation between CSF volume or dural sac surface area and peak sensory block level estimated that a 5- to 6-mL difference in CSF volume and a 0.7-cm² difference in dural sac surface area result in a 1-segment difference after spinal or epidural anesthesia.¹⁰⁻¹² These findings and the results of this study suggest that the reduction in CSF volume and dural sac surface area in third-trimester pregnant women might explain a 1-segment increase in sensory block level in the third trimester of pregnancy, although the precise CSF volume or dural sac surface area required to produce a 1-segment difference in spinal or epidural anesthesia is unclear. In previous studies, a 2- to 2.5-segment difference in the maximum cephalad extent of spinal anesthesia was reported between nonpregnant and third-trimester pregnant women.³⁻⁵ This observation suggests that the reduction in CSF volume in pregnant

women at term is insufficient to entirely explain the facilitation of spinal anesthesia. In addition, the facilitated spread of neuraxial block in pregnant women occurs as early as the end of the first trimester.^{1,2} Fagraeus et al.² reported a 4-segment difference in epidural anesthesia between nonpregnant and first-trimester pregnant women. Although epidural blood vessels become engorged even during the first trimester,¹⁶ it is unlikely that compression of the dural sac by epidural venous distention has a significant role in the first trimester. These findings, therefore, suggest the involvement of another mechanism besides dural sac compression, such as another anatomic, biochemical, or hormonal mechanism.

There are several limitations to this study. First, the MRI examinations for the measurement of lumbosacral CSF and dural sac surface area were only performed with the women in a supine position without uterine tilting. Hirabayashi et al.¹⁷ reported that when the parturients (33 wk gestation) turned to the left-lateral position, the engorged anterior internal vertebral veins shrank in the lateral position. With respect to the change in lumbosacral CSF and dural surface area, the results in the supine position might differ from other positions, such as the left-lateral tilt position. Second, because the boundaries of the adjacent structures are not clear because of the limited resolution of MRI scans, and axial slices obtained for the measurement of CSF volume and dural sac surface area are not contiguous (5-mm intervals), there are many sources of error in calculating CSF volume and dural sac surface area. Although the method we used for measuring was validated in a previous study by measuring known volumes with reliable duplication with repeated measurements,¹³ improved slice spatial resolution with new MRI technology will increase the accuracy and precision of the measurement of CSF volume and dural sac surface area. Third, the CSF volume measured using these MRI techniques included the cauda equina. This, however, contributes to only approximately 15% of the total volume of the dural sac at this level,¹⁸ and it is unlikely that the size of the cauda equina changes with pregnancy. Fourth, the level of the disk between the 11th and 12th thoracic vertebrae was the reference point for the measurement of CSF volume and dural sac surface area in both the nonpregnant and pregnant states. Axial images below this level did not necessarily match between the nonpregnant and pregnant states because of the changes in the curvature of the spinal column with pregnancy. The apex of lumbar lordosis was caudad, and thoracic kyphosis was reduced in the supine position in the later stages of pregnancy.¹⁹ Therefore, these changes may affect the comparison of the CSF volume and dural sac surface area in the nonpregnant state with those in the pregnant state. Finally, in 14 of 18 women, MRI examinations in the nonpregnant state were performed after parturition. Although the uterus and maternal blood volume return to their

previous nonpregnant size or level within approximately 6 wk,²⁰ there is no evidence that the veins and fat surrounding the uterus return to their previous nonpregnant state within a few months. Further study is therefore required.

In summary, this study confirms a third-trimester, gestation-related reduction in CSF volume and dural sac surface area. These findings were associated with engorged epidural veins. This may explain, at least in part, the increase in the sensory level of neuraxial block observed in pregnant women.

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Up-Down Determination of the 90% Effective Dose of Phenylephrine for the Treatment of Spinal Anesthesia-Induced Hypotension in Parturients Undergoing Cesarean Delivery

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INTRODUCTION: Hypotension frequently complicates spinal anesthesia for cesarean delivery, and vasopressors are the mainstay for treatment. The most effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension has not been estimated.

METHODS: Healthy nonlaboring women undergoing a cesarean delivery were recruited. All women received spinal anesthesia using hyperbaric bupivacaine 12 mg with fentanyl and morphine. Each subject received an IV crystalloid fluid bolus before and at the time of initiation of spinal anesthesia (preload and coload). An up-down sequential allocation method using the biased-coin design was used to estimate the 90% effective dose (ED₉₀) of phenylephrine. The assigned phenylephrine dose was based on the response of the preceding subject. If the systolic blood pressure (SBP) decreased >20% of baseline (i.e., SBP 20%) or to an SBP <90 mm Hg, the assigned dose of phenylephrine was administered. If the SBP returned to within 20% of baseline or ≥90 mm Hg within 1 min, this was considered a success, otherwise it was a failure. The initial dose of phenylephrine was 100 μg. The ED₉₀ with 95% confidence intervals (CIs) was calculated using the maximum likelihood estimation and Firth logistic regression.

RESULTS: Sixty-nine subjects were screened to participate, of whom 66 subjects consented. Forty-five of the enrolled subjects experienced spinal anesthesia-induced hypotension and received a blinded dose of phenylephrine. Those subjects who developed hypotension received doses of phenylephrine between 80 and 180 μg. No subjects experienced hypertension. Determined with the maximum likelihood estimation method, the ED₉₀ of phenylephrine was 147 μg (95% CI, 98–222 μg). With Firth regression, the probability of a successful response at 150 μg is 90.5% (95% CI, 66.0%–99.0%).

CONCLUSION: In this study, we estimated that the ED₉₀ of phenylephrine required to treat spinal anesthesia-induced hypotension in cesarean delivery is approximately 150 μg. (Anesth Analg 2010;110:154–8)

Spinal anesthesia for cesarean delivery is frequently complicated by hypotension with a reported incidence of up to 80%.¹ Spinal anesthesia has been associated with a greater risk of fetal acidosis during cesarean delivery compared with epidural and general anesthesia.^{2,3}

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Vasopressors are the mainstay for the prevention and treatment of hypotension associated with spinal anesthesia. Phenylephrine and ephedrine are routinely used to treat spinal anesthesia-induced hypotension. Fetal outcomes assessed by umbilical arterial and venous pH are improved, and maternal nausea and vomiting reduced if maternal systolic blood pressure (SBP) is maintained at its baseline level with phenylephrine compared with ephedrine.^{1,4,5} However, the optimum dose of phenylephrine for the treatment of hypotension has not been determined. In this double-blind, up-down study, we sought to estimate the 90% effective dose (ED₉₀) of IV phenylephrine for the treatment of hypotension associated with spinal anesthesia for cesarean delivery.

METHODS

Institutional research ethics board approval was obtained. The trial was registered at www.clinicaltrials.gov (NCT00781157). Adult (age ≥18 yr), ASA physical

status I and II, nonlaboring women undergoing an elective cesarean delivery with spinal anesthesia at term with singleton gestation (37–42 wk) were recruited. Exclusion criteria were morbid obesity (body mass index ≥ 45 kg/m²), height <152 cm, history of severe hypertensive disease of pregnancy (SBP >160 mm Hg, diastolic blood pressure >110 mm Hg, and/or requirement for antihypertensive treatment or presence of significant proteinuria), and significant maternal cardiac disease or diabetes.

After obtaining written informed consent and before entering the operating room, subjects had their arterial blood pressure measured 3 times (every 2 min), supine with left uterine displacement. The mean of the 3 SBP readings was deemed the baseline SBP. Hypotension was defined as SBP <20% of baseline or SBP <90 mm Hg.

All women received spinal anesthetic administered between L3 and L5 in the sitting position using hyperbaric bupivacaine 12 mg, fentanyl 15 μ g, and preservative-free morphine 100 μ g. Subjects were immediately laid supine with left uterine displacement. Each subject received an IV preload and coload of lactated Ringer's solution (approximately 15–20 mL/kg) with the aim of administering 500 mL before spinal anesthesia and 2 L before delivery. After the spinal anesthetic procedure was completed, arterial blood pressure was measured every minute for 10 min and then every 2.5 min for the duration of the study. If the study medication was administered, arterial blood pressure was measured every minute until SBP returned to within 20% of baseline.

If the SBP decreased >20% of baseline or to an SBP <90 mm Hg, a 5-mL syringe with saline and a predetermined dose of phenylephrine was administered. An anesthesiologist not involved with patient recruitment, anesthetic care, or data collection prepared the coded syringes of phenylephrine. If the SBP returned to within 20% of baseline or ≥ 90 mm Hg within 1 min, treatment was considered a success. Any resultant hypertension (SBP >20% above baseline) was noted but not considered a failure. If hypotension persisted after 1 min, the anesthesiologist treated the hypotension with a vasopressor of his or her choice. This was recorded as a failure. The study concluded with the response to the blinded phenylephrine bolus or delivery, whichever occurred first.

The initial dose of phenylephrine was 100 μ g. This dose was chosen based on our clinical experience and statistical simulation at various doses. Each subsequent dose was based on the response of the preceding subject, as per a biased-coin design up-down sequential method.⁶ The dosing changes were in increments of 20 μ g. The anesthesia provider was blinded to the dose of phenylephrine, as was the subject. If a failure was observed in the previous subject, the dose was stepped up in the next subject. If a success was observed, the next subject was randomized with probability of 0.1 to the next lower dose and

with probability of 0.9 to the same dose.* If no hypotension occurred before the birth of the neonate, the subject was withdrawn and the next subject was assigned the same dose.

The ED₉₀ with 95% confidence intervals (CIs) and estimated probabilities were calculated using maximum likelihood estimation (MLE) and Firth logistic regression with penalized MLE using Minitab 15 (Minitab, State College, PA) and LogXact 8.0 (Cytel, Cambridge, MA).⁷ A sample size of at least 40 patients was selected after testing a variety of scenarios, each with a million simulations of both the responses and the corresponding doses selected by the sequential allocation method described above, and beginning with various starting doses.

RESULTS

Sixty-nine subjects were screened to participate in this study (Fig. 1). Three subjects were excluded before consent. Sixty-six subjects consented; however, 1 subject was withdrawn before the spinal anesthetic because she received atropine to treat a vasovagal response to local infiltration in preparation for the anesthetic procedure. Of the 65 subjects who completed the trial, 20 (31%) did not experience hypotension and were withdrawn from the study.

Forty-five enrolled subjects (69%) experienced spinal anesthesia-induced hypotension and received phenylephrine per study protocol. There was no difference in age, weight, height, crystalloid volume, or sensory level between women who became hypotensive and received phenylephrine compared with those who did not (Table 1).

Those subjects who developed hypotension received doses of phenylephrine ranging between 80 and 180 μ g with failures noted in all dosages except for 180 μ g (Fig. 2). Of the 45 subjects who experienced hypotension and received a bolus of phenylephrine, the mean reduction in SBP was 25% \pm 7% from the baseline SBP. No subjects experienced hypertension (SBP >20% above baseline) after receiving the allocated phenylephrine dose. The time (mean \pm SD) from spinal anesthesia administration to hypotension was 5.8 \pm 3.6 min. Determined with the MLE method with raw data, the ED₉₀ of phenylephrine was 147 μ g (95% CI, 98–222 μ g) (Fig. 3). Using Firth regression, the probability of a successful response at 150 μ g is 90.5% (95% CI, 66.0%–99.0%) (Fig. 4).

Two subjects who received phenylephrine boluses for hypotension required treatment of bradycardia. The first subject was a treatment failure (phenylephrine 140 μ g) and received atropine for a heart rate of 55 bpm and hypotension. The subject's arterial blood

*The probability $P = (1 - \gamma)/\gamma$. For $\gamma = 0.9$, then $P = 0.1/0.9$, thus if a positive response is observed, then the dose for the next patient is assigned at probability 1/9 to the next lower dose and probability 8/9 to the same dose. These values were rounded to the nearest tenth, i.e., 0.1 and 0.9.

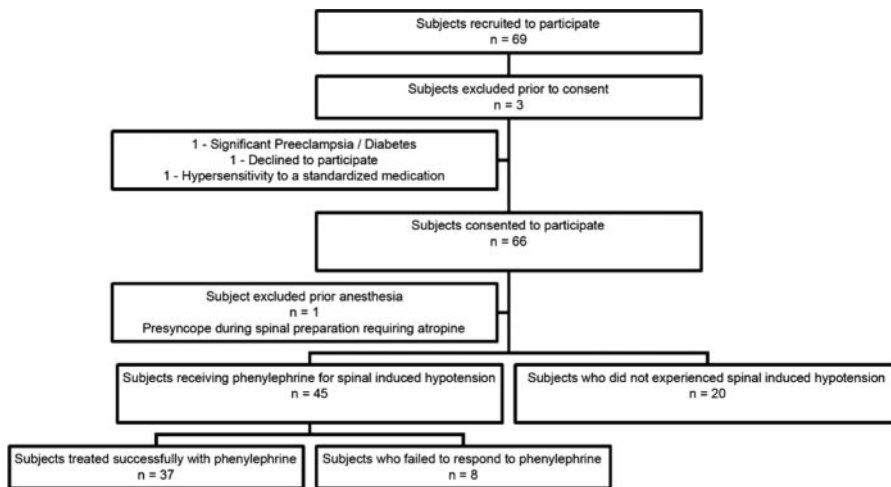


Figure 1. Subject cohort flow diagram.

Table 1. Patient Demographics and Operative Variables

| Variable | Hypotensive subjects n = 45 | Nonhypotensive subjects n = 20 |
|--------------------------------------|--------------------------------|-----------------------------------|
| Age (yr) | 34 ± 5 | 31 ± 6 |
| Weight (kg) ^a | 86 ± 15 | 90 ± 13 |
| Height (cm) | 163 ± 7 | 162 ± 5 |
| Body mass index (kg/m ²) | 32.3 ± 5.3 | 33.9 ± 4.4 |
| Estimated gestational age (wk) | 39 (39, 39) | 39 (38, 39) |
| Crystalloid volume (mL) | 1933 ± 222 | 1911 ± 179 |
| Estimated blood loss (mL) | 481 ± 183 | 542 ± 181 |
| Sensory block at 5 min ^b | T4 (T4, T5) | T5 (T4, T6) |
| Sensory block at 10 min ^b | T3 (T3, T4) | T4 (T3, T4) |

No statistical significance between hypotensive and nonhypotensive subjects.

Data presented as mean ± SD or median (IQR).

IQR = interquartile range.

^a Term pregnancy weight.

^b Pinprick sensation.

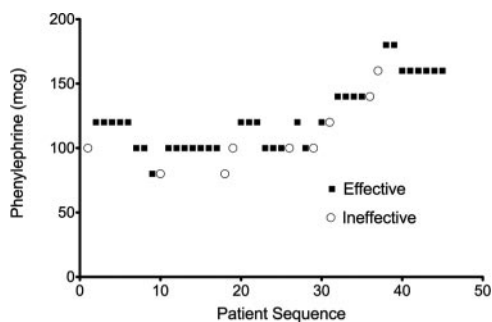


Figure 2. Frequencies of doses of phenylephrine, patients' responses, and subsequent dose allocations.

pressure returned within 20% of baseline after receiving atropine with no subsequent hypertension. The second subject was a treatment success (phenylephrine 160 μg) and received glycopyrrolate for a heart rate of 49 bpm without hypotension. There was no reactive hypertension after the administration of glycopyrrolate.

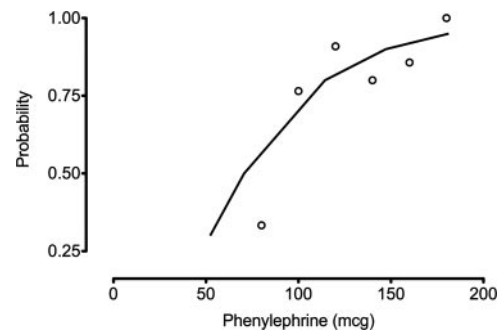


Figure 3. Observed probabilities (○) of successful responses to phenylephrine doses using logistic regression and maximum likelihood estimation of raw data (95% confidence interval, 98–222 μg).

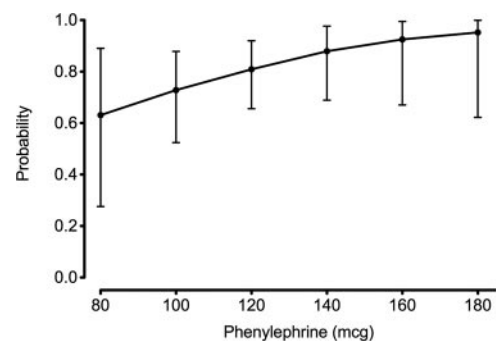


Figure 4. Fitted probabilities of successful responses at the specific phenylephrine doses tested using Firth regression with profile likelihood 95% confidence intervals.

DISCUSSION

In this study, we found that the ED₉₀ of phenylephrine bolus required to reverse hypotension induced by spinal anesthesia in cesarean delivery is 147 μg. This dose is 50% more than our suspected results and what is typically reported in clinical use. Although the 95% CIs span over 100 μg, it is worth noting that our current clinical dose is at the bottom end of this CI. As evidenced by lack of maternal hypertension and significant bradycardia, our study agrees with previous study results suggesting that doses of phenylephrine in this range are unlikely to have any negative impact

Table 2. Results Using Isotonic Regression Estimation and PAVA Approach

| Dose (mg) | Successes (n) | Trials (n) | Probability (observed) | Probability (PAVA) |
|-----------|---------------|------------|------------------------|--------------------|
| 80 | 1 | 3 | 0.33 | 0.33 |
| 100 | 13 | 17 | 0.76 | 0.76 |
| 120 | 10 | 11 | 0.91 | 0.87 |
| 140 | 4 | 5 | 0.80 | 0.87 |
| 160 | 6 | 7 | 0.86 | 0.87 |
| 180 | 2 | 2 | 1.00 | 1.00 |

PAVA = pooled adjacent violators algorithm.

on neonatal or maternal outcomes.⁸ Recently, Tanaka et al.⁹ estimated the 95% effective dose (ED₉₅) of a phenylephrine bolus to prevent spinal anesthesia-induced hypotension and nausea to be 135 and 159 μ g, respectively. The results of Tanaka et al.⁹ and those of our trial suggest that the doses of phenylephrine required to prevent and treat hypotension are higher than previously suspected, suggesting that further evaluation of phenylephrine in this dose range is warranted.

Hypotension during spinal anesthesia is common, and nonpharmacologic measures to combat hypotension are frequently not effective.^{10–12} Vasopressors such as ephedrine and phenylephrine are frequently required whether or not aggressive fluid management is part of prophylaxis of spinal anesthesia-induced hypotension. Ephedrine is no more effective than phenylephrine and may result in a lower umbilical cord pH compared with phenylephrine.^{4,5,13,14} However, the increased fetal oxygen consumption and excretion of carbon dioxide observed by Ngan Kee et al.⁴ as the dose of ephedrine increased may reflect a direct fetal effect of ephedrine increasing fetal metabolism. Phenylephrine, perhaps because of preferential maternal splanchnic vasoconstriction over uterine artery vasoconstriction, may increase maternal cardiac output and improve uteroplacental circulation.¹⁵

Earlier up-down methodology studies sought the ED₅₀ of various drugs, e.g., the dose of inhaled anesthetics that by definition is effective in 50% of subjects. Anesthesiologists were left to extrapolate the ED₅₀ to more clinically useful doses, i.e., ED₉₀ or ED₉₅ that would be effective in 90%–95% of patients. The biased-coin design allows the researchers to set the quantile effect dose of interest, i.e., 90%, 95%, or even 50% if they choose. Our preliminary simulations, designed to guide our project, led us to the conclusion that the ED₉₀ would give us reasonably precise results. Although striving for the ED₉₅ may be more clinically relevant, we believed this would sacrifice precision of our estimate. Despite this, we do not want to overstate our precision. Table 2 shows results from our data using isotonic regression estimation and the pooled-adjacent-violators algorithm approach. This demonstrates breaches of monotonicity (i.e., as the dose increases, the drug effect increases) that can occur with such data. These approaches can be used to

provide better precision and narrower CIs for point estimates. However, given the unpredictability of the degree of hypotension associated with the initiation of spinal anesthesia for cesarean delivery (i.e., wide variance in change of SBP from baseline), such natural variability in response is not surprising. Therefore, we prefer to use the more conservative approach and emphasize the inherent uncertainty by reporting with wider precision.

Our results may have been influenced by our decision to use the 1-min mark to judge the effectiveness of phenylephrine. The peak action of centrally administered phenylephrine is 30–45 s,¹⁶ and therefore we believe that the 1-min interval for peripherally administered phenylephrine was an appropriate interval. Additionally, in this clinical scenario, if hypotension has not resolved within 1 min, most obstetrical anesthesiologists would typically opt for alternate or additional therapy. Furthermore, we note in our study that those subjects who failed treatment with the allocated phenylephrine dose and received additional therapy did not have any subsequent hypertension. This suggests that they likely required a higher dose than the allocated study treatment dose and truly would have failed treatment no matter how long we waited. This study concluded with delivery of the neonate, and therefore the results are applicable to the hypotension associated with the evolution of the spinal blockade in pregnant women with high thoracic neuroblockade. The study also was restricted to the treatment of the first episode of hypotension. Therefore, these results may not be generalizable to recurrent episodes of hypotension that may occur at a later stage of the anesthetic when the block has stabilized, or to hypotension associated with oxytocin administration or blood loss.

In conclusion, the estimated ED₉₀ of phenylephrine for the treatment of hypotension after spinal anesthesia for cesarean delivery is approximately 150 μ g. Recognizing that the 95% CI of the ED₉₀ is between 98 and 220 μ g, our traditional starting dose of 100 μ g may be reasonable; however, efficacy may be improved by starting with a higher dose. Based on our results, further evaluations of phenylephrine in this dose range are warranted.

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A Randomized, Double-Blind, Placebo-Controlled Trial of Epidural Morphine Analgesia After Vaginal Delivery

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BACKGROUND: Pain after vaginal delivery can interfere with the activities of daily living. We hypothesized that epidural medication administered after delivery would be of benefit for acute postpartum pain management. The objective of this study was to assess whether epidural morphine after vaginal delivery would reduce the analgesic requirements for perineal pain.

METHODS: This randomized, double-blind, placebo-controlled trial included 228 parturients who received epidural morphine, 2.5 mg, or epidural saline within 1 h of delivery. The primary outcome was the proportion of women who received additional analgesics in the first 24 h postpartum. We also evaluated the time to first request for analgesia, pain and satisfaction scores, and the incidence of side effects due to epidural morphine.

RESULTS: The majority of the 228 women participating in the study were Caucasian, primiparous patients >30 yr old. The proportion of women requiring additional analgesics was less among those who received epidural morphine (8 of 113; 7%) compared with saline (37 of 115; 32%), regardless of the degree of perineal trauma (RR = 0.22, 95% CI: 0.12–0.41). The relative risk reduction in receiving additional analgesics for primiparous patients receiving epidural morphine compared with saline was 0.25 (95% confidence interval [CI]: 0.13–0.49) and for multiparous women was 0.12 (95% CI: 0.02–0.63). The time to first request for analgesics was later for those who received morphine (mean 22.9 h, 95% CI: 22.2–23.7) compared with saline (mean 18.9 h, 95% CI: 17.4–20.4) ($P < 0.0001$). The side-effect incidence (pruritus, nausea and vomiting, and sedation) was not different between the 2 groups.

CONCLUSION: There was a 78% reduction in analgesic requirements in women given epidural morphine after vaginal delivery compared with placebo for both primiparous and multiparous patients. Women who receive epidural labor analgesia for vaginal deliveries and stay in the hospital for 24 h after delivery may benefit from postpartum administration of epidural morphine.

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In a previous study from our institution, we found that even women with little perineal trauma after vaginal delivery report significant interference in common daily activities, such as sitting and urinating, due to postpartum perineal pain.¹ Thirty-seven percent of women with no perineal trauma or first-degree perineal lacerations described their perineal pain on the first day postpartum as distressing, horrible, or excruciating.¹ The use of systemic, multimodal analgesics in

the postpartum period is increasing as physicians recognize the safety and utility of drugs such as nonsteroidal antiinflammatory drugs and acetaminophen.² However, systemic opioids are often required to achieve satisfactory analgesia, but at our institution these were only considered for women with extensive perineal trauma, such as third- or fourth-degree lacerations. Before this study, our institution's practice for analgesia after vaginal delivery was intermittent, administered-as-requested oral, IM, or IV medications.

As a follow-up to our previous study of acute postvaginal perineal pain, we hypothesized that all women using epidural labor analgesia would benefit from a single dose of postpartum epidural morphine. The basis of our hypothesis stemmed from the success of epidural and intrathecal morphine for postcesarean analgesia, and its routine use in North American obstetric anesthesia units.³ Epidural and intrathecal administration of morphine has the benefit of profound, prolonged analgesia at relatively low doses. The benefits compared with systemic opioids have been demonstrated in many postoperative analgesic settings.^{4,5} The objective of this study was to determine whether a single dose of epidural morphine

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given soon after a vaginal delivery would reduce postpartum perineal pain and reduce the use of IV or oral opioid analgesics in the early postpartum period.

METHODS

This single-center, randomized, double-blind, clinical trial received IRB approval and was conducted at Mount Sinai Hospital, Toronto. Women eligible for inclusion in the study were those who delivered vaginally and who had received effective epidural analgesia for labor and delivery. Their informed, written consent to be involved in the study was obtained before delivery. Women receiving combined spinal-epidural analgesia for labor were excluded. The labor analgesia was not standardized for patients in the study but usually consisted of the following practice. Epidural analgesia was initiated with epidural bupivacaine 0.1%–0.125% and 50–100 μg of fentanyl, followed by a patient-controlled epidural analgesic with bupivacaine 0.0625% and fentanyl 2 $\mu\text{g}/\text{mL}$. Settings for the patient-controlled epidural analgesic pump included a background infusion between 8 and 10 mL/h, demand bolus of 5 mL, and lockout interval of 5–10 min. The infusion was continued until perineal suturing was finished.

The randomization schedule was stratified for primiparous and multiparous study subjects using a computer random number generator to select random permuted blocks of 8. The pharmacy department independently created the schedule and prepared sterile syringes of either epidural morphine or epidural saline in batches of 10 with assigned random numbers. Within 1 h of delivery, study subjects were randomized to receive 1 of 2 identical-appearing syringes epidurally with either preservative-free morphine 2.5 mg diluted to 10 mL, or 10 mL of preservative-free saline. The epidural catheter was removed just before the patient's transfer to the postpartum ward.

A standard anesthesia order set with monitoring, side-effect therapy, and analgesic guidelines was used for 24 h after discharge to the postpartum ward. Patients were monitored every hour for the first 12 h and every 2 h for the second 12 h by the nursing staff for sedation level, pruritus and nausea/vomiting, and visual analog scale (VAS) score for pain. All patients received scheduled acetaminophen (1000 mg every 6 h) and ibuprofen (400 mg every 6 h). In addition, women could request additional analgesics (opioids) for breakthrough perineal pain. The additional opioids included oral codeine (30–60 mg every 6 h as requested) or IM morphine (5–10 mg every 4 h as requested). The choice of supplemental opioid was made in cooperation with the patient and her nurse. Assessment of supplemental analgesia requirements was a 2-step process: patient and nursing opioid records were assessed at 24 h postpartum for counts of additional analgesics, and all patients were asked whether they

had received supplemental medications beyond the acetaminophen and ibuprofen.

The primary outcome was the proportion of women in each group who received opioid analgesia in the first 24 h postpartum. Secondary outcomes included maternal VAS pain score at time of first request, using a 10-cm line anchored at 0 with the words "no pain" and the other end "worst pain imaginable," maternal satisfaction with perineal analgesia during the first 24 h postpartum (5-point Likert scale), time to first request for supplemental analgesia after delivery, and the incidence of side effects in the first 24 h postpartum, including pruritus, nausea and vomiting, drowsiness, and urinary retention. Study participants were asked by nursing staff every 4 h whether they had pruritus, nausea or vomiting (yes or no), and were assessed for presence of drowsiness. Drowsiness was defined as respiratory rate <10 breaths/min or visual presence of moderate sedation or somnolence as assessed by the participant's nurse. Urinary retention was defined by the need for catheterization. Women with indwelling catheters placed immediately after delivery were excluded from this analysis. Subjects were telephoned 1 wk postpartum to assess whether any nonopioid or opioid analgesics were taken since hospital discharge.

Information on potential confounding variables was collected, including parity, gestational age, type of vaginal delivery (spontaneous or operative vaginal delivery, indicating use of vacuum or forceps), degree of perineal trauma as reported in the hospital delivery record, neonatal birth weight, maternal age, maternal body mass index, and self-identified cultural background (5-category scale of heritage used by Census of Canada). Perineal trauma was classified as minor and major trauma. Minor trauma was defined as no lacerations, periurethral lacerations, and first-degree lacerations. Major trauma was defined as second-, third-, and fourth-degree lacerations and episiotomies.

Sample size calculation was based on the incidence of women requiring opioid analgesia in the first 24 h postpartum who had no identified perineal trauma. This incidence was estimated at 63% in a previous study from our institution,¹ and we wished to detect a 30% reduction in opioid analgesic use in the group of women who received epidural morphine compared with the epidural saline group (absolute difference of 19%). Using sample size calculations based on proportions using a 2-sided test, and accepting a type I error rate of 0.05 and a type II error rate of 0.20, 107 women were required in each group, with planned recruitment of 230 women for the study.

Adequacy of randomization was assessed by examining for any differences in the distribution of potential confounding variables in the 2 groups using the Student's *t*-test and Fisher's exact test for differences in means and proportions, respectively. A crude relative risk (RR) estimate for the analgesic-sparing effect

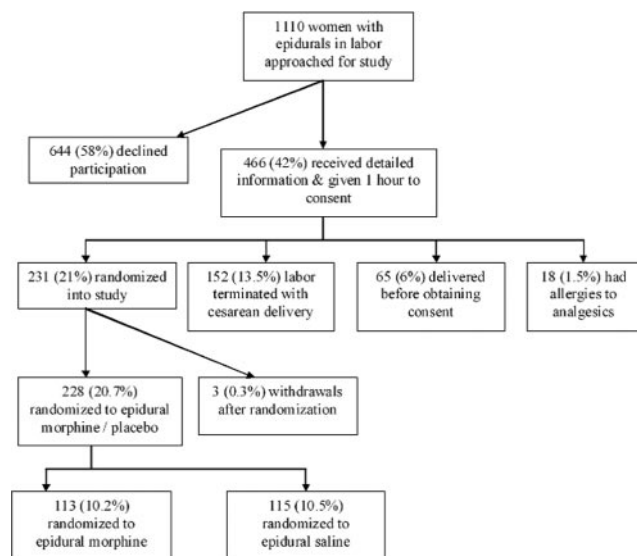


Figure 1. CONSORT recommended description of patient recruitment to the epidural morphine randomized, double-blind, placebo-controlled trial at Mount Sinai Hospital, Toronto, Canada.

of epidural morphine compared with placebo was calculated with 95% confidence intervals (CIs) as well as an adjusted estimate, adjusting for degree of perineal trauma and parity. Fisher's exact test for difference in proportions was used to compare the incidence of the primary and secondary outcomes. Time to first request for supplemental opioid analgesia was assessed using survival analysis, and other continuous variables were compared using the Student's *t*-test for difference in means. Significance level for the primary outcome was defined as $P < 0.05$, whereas secondary outcome P values were adjusted using Bonferroni corrections for multiple testing. All analyses were done using the program STATA (version 8.2, Stata-Corp, College Station, TX).

RESULTS

After the successful initiation of a labor epidural analgesia, 1110 women were approached and given information regarding the study between March 2002 and November 2004. Consent to participate in the study was obtained before delivery. Figure 1 provides the CONSORT flow diagram on the participation of women approached for the study and reasons for non-participation in the study.⁶ Less than 50% of the women gave consent to participate in the study if they delivered vaginally. The majority of nonparticipants declined participation because of reticence in receiving an opioid prophylactically. Two hundred twenty-eight women who delivered vaginally were randomized to receive epidural morphine ($n = 113$) or saline ($n = 115$). There was no difference in the demographic variables between groups (Table 1). Women participating in the study were primarily Caucasian primiparous patients, with an average maternal age of

Table 1. Demographic Variables

| Variable | Epidural morphine (N = 113) | Epidural saline (N = 115) | P |
|--|-----------------------------|---------------------------|------|
| Primiparous <i>n</i> (%) | 76 (67%) | 79 (69%) | 0.89 |
| Maternal age (yr) | 32 (4.9) | 32 (4.9) | 0.66 |
| Maternal body mass index (kg/m ²) | 29 (5.9) | 29 (6.6) | 0.99 |
| Maternal ethnicity | | | |
| Caucasian | 87 | 99 | 0.22 |
| Asian | 8 | 6 | |
| Latin American | 4 | 3 | |
| Arabic | 3 | 1 | |
| Black | 2 | 1 | |
| Not stated | 9 | 5 | |
| Gestational age (wk) | 39.3 (1.7) | 38.8 (3.8) | 0.22 |
| Neonatal birthweight (kg) | 3.4 (0.5) | 3.4 (0.5) | 0.84 |
| Perineal trauma | | | |
| First degree or less | 31 (27%) | 28 (24%) | 0.65 |
| Second degree or greater | 82 (73%) | 87 (76%) | |
| Operative vaginal delivery | 38 (34%) | 34 (30%) | 0.57 |
| VAS pain score at study drug administration (0–10) | 1.2 (1.8) | 1.5 (2.0) | 0.24 |

Values are reported as *n* (%) or mean (sd).

VAS = visual analogue scale.

>30 yr. One-third of study participants had an operative vaginal delivery and 169 of 228 (74%) women had major perineal trauma. The mean maternal VAS pain score just before administration of the study drug was <2, indicative of residual epidural analgesia after delivery.

The number of women who required additional analgesics in the first 24 h after vaginal delivery was 8 of 113 in the epidural morphine group compared with 37 of 115 in the epidural saline group ($P < 0.001$). This is a 78% reduction in the risk of opioid analgesia requirement among women who received epidural morphine compared with saline (RR 0.22, 95% CI: 0.12–0.41). This risk reduction with the administration of epidural morphine was consistent among both primiparous (RR 0.25, 95% CI: 0.13–0.49) and multiparous women (RR 0.12, 95% CI: 0.02–0.63) (Table 2). Among the women with differing degrees of perineal trauma, the effect of analgesic sparing seemed to remain consistent. For women with minor perineal trauma, the RR reduction in the requirement for opioid analgesics was 85% (RR 0.15, 95% CI: 0.03–0.86), and among those with major trauma, the risk reduction was 73% (RR 0.27, 95% CI: 0.14–0.50). RR estimates for reduction of epidural morphine in analgesic requirements remained unchanged when adjusted for degree of perineal trauma and parity (adjusted odds ratio 0.16, 95% CI: 0.07–0.36).

The VAS pain scores at time of first request for supplemental opioid were similar between the 2 groups. The time to first request for an additional opioid analgesia was prolonged among women receiving epidural morphine by 4 h ($P < 0.001$). The

Table 2. Analgesia and Side Effects

| Outcomes | Epidural morphine (N = 113) | Epidural saline (N = 115) | P |
|---|-----------------------------|---------------------------|--------|
| Supplemental analgesia, n/N (%) | | | |
| Stratified by parity | 8/113 (7%) | 37/115 (32%) | <0.001 |
| Primiparous | 7/76 (9%) | 29/79 (37%) | <0.001 |
| Multiparous | 1/37 (3%) | 8/36 (22%) | 0.01 |
| Time to first request for additional analgesic (h) | 22.9 (4.0) | 18.9 (8.0) | <0.001 |
| VAS pain score at time of first request for additional analgesic (cm) | 5.2 (2.1) | 4.6 (2.6) | 0.51 |
| Maternal satisfaction ^a , n/N (%) | | | |
| Strongly disagree/disagree | 10/104 (13%) | 14/105 (10%) | 0.80 |
| Not sure | 6/104 (8%) | 8/105 (6%) | |
| Strongly agree/agree | 78/104 (79%) | 83/105 (84%) | |
| Side effects, n/N (%) | | | |
| Pruritus | 13/108 (12%) | 6/109 (6%) | 0.10 |
| Nausea | 10/107 (9%) | 5/109 (5%) | 0.20 |
| Drowsiness | 2/106 (2%) | 0/107 (0%) | 0.25 |
| Urinary retention | 20/109 (18%) | 11/111 (10%) | 0.08 |

Data presented as n/N (%) or mean (sd).

VAS = visual analogue scale.

^a Study subjects were asked to rate the following question of satisfaction with perineal analgesia at 24 h postdelivery: "I was satisfied with my pain relief in my bottom during the first day."

average time to request supplemental opioid analgesia among women who requested additional analgesia was 8 h after delivery. Estimation of maternal satisfaction with perineal pain management was completed at 24 h postpartum by 209 of the 218 women. Maternal satisfaction was not different between the groups.

The incidence of side effects did not differ between the groups. The most common side effect was urinary retention, among 14% of the study population. The proportion of women reporting pruritus to their nurses was 9% overall. Nausea, defined as the number of women receiving antiemetics in the first 24 h, occurred in 7% of all women. Only 1% of the study population met the definition of drowsiness.

During the first week postpartum, analgesic use was evaluated among 203 women. Among women receiving epidural morphine, 81% (79 of 98) used analgesics, including opioids and nonopioids, compared with 69% (72 of 105) of women receiving epidural saline ($P = 0.06$).

DISCUSSION

Women receiving 2.5 mg of epidural morphine after a vaginal delivery reduced their use of opioid analgesics by 78% compared with women receiving placebo in the first 24 h postpartum. We believe that the benefit of epidural morphine was underestimated

because our control group received improved postpartum perineal pain management compared with what occurs normally on our postpartum wards. The entire study population received scheduled doses of acetaminophen and ibuprofen during the first 24 h, which has not been routine in the past. Before the study, patients received a bedside pack of acetaminophen and ibuprofen for self-administration. Therefore, if we had used our standard of postpartum pain care for the control group, the risk reduction with morphine use would likely have been even greater.

Although vaginal deliveries seem inherently to be associated with less pain than cesarean delivery, recent evidence has contradicted this belief. Eisenach et al.⁷ have demonstrated in a prospective study of 1288 women that acute postpartum pain is associated with development of persistent pain at 8 weeks' postpartum, regardless of the mode of delivery. The authors identified an independent risk (RR 2.5) for development of persistent postpartum pain; if severe, acute postpartum pain was present. It seems reasonable to apply principles of analgesic management to all women who deliver, because the individual's pain response to trauma injury may not be correlated with degree of trauma. It remains to be proven whether limiting or eliminating severe, acute postpartum pain can reduce the development of chronic pain syndromes. Beyond providing excellent intrapartum pain relief with epidural analgesia, the availability of excellent postpartum analgesia may be an additional benefit available to women who choose epidural labor analgesia.

To our knowledge, there are 4 other randomized trials evaluating epidural morphine for postvaginal delivery pain,^{8,9,*†} 2 of which are only reported as abstracts.*† Table 3 outlines the characteristics and results of 4 studies, along with this study. Women were randomized to receive doses of 1–4 mg of epidural morphine or epidural saline. In our study, the choice of a 2.5-mg dose of epidural morphine was made based on evidence documenting the effectiveness of this dose for postcesarean analgesia¹⁰ and the early work by Macdonald and Smith⁸ in postepisiotomy pain. The study of Macdonald and Smith⁸ evaluated only women with episiotomies because the investigators thought that this degree of perineal trauma necessitated additional analgesia. The 2 largest studies^{8,9} and our study had the highest quality ($\geq 4/5$ Jadad score¹¹) and found a similar drug-sparing effect in the epidural morphine compared with saline groups. The 2 small studies*† reported only as abstracts did not find a reduction in maternal VAS pain scores during the first 24 h postpartum. This may have

*Ascanio RS, Mahaney G, Sarna MC, Soni AK, Oriol NE. A single dose of epidural morphine alleviates post-partum perineal pain for at least one week. SOAP 1997:A153.

†Nunlee WY, Perry PM, Lawal AH, Ivankovich AD. Does a single dose of epidural morphine provide extended analgesia after vaginal delivery? Anesthesiology 2000:A160.

Table 3. Randomized Clinical Trials Evaluating Epidural Morphine After Vaginal Delivery

| | Macdonald and Bickford Smith ⁸ | Ascanio et al. ^a | Nunlee et al. ^b | Goodman et al. ⁹ | Current study |
|----------------------------------|---|---|--|---|--|
| Study size | N = 124 | N = 20 | N = 30 | N = 81 | N = 228 |
| Jadad quality score ^c | 4/5 | 3/5 | 3/5 | 5/5 | 5/5 |
| Type of perineal trauma | Only episiotomy | All | All | All | All |
| Epidural morphine dose | 2 or 4 mg | 2 mg | 2 mg | 1 or 2 mg | 2.5 mg |
| Primary outcome | Not stated | Not stated | Not stated | Opioid dose in first 24 h postpartum | Incidence additional analgesics first day postpartum |
| Secondary outcomes | VAS pain scores at 1, 4, 8, 12, 24, 36 h; additional analgesics | VAS pain scores at 1, 2, 6, 12, 24, 48 h; additional analgesics; side effects; 1-wk follow-up | VAS pain scores at 2, 4, 8, 24 h; additional analgesics; side effects; 2, 4, 7 day follow-up | VAS pain scores at 1, 2, 6, 12, 18, 24 h; maternal satisfaction; side effects; 1-wk follow-up | Time to first request for analgesics; VAS pain score at time of request; maternal satisfaction |
| Analgesic findings | VAS pain scores and analgesics requirements less during first 12 h for 2- and 4-mg groups | VAS pain scores and analgesic requirements less during 48 h for morphine group | No difference in pain scores or supplemental analgesics between groups | Reduction in average oral opioid dose in first 24 h; no difference in pain scores | 80% reduction in incidence of additional analgesics; longer time to first analgesia request |
| Side effects findings | Morphine group: Dose-dependent pruritus; nausea | Morphine group: pruritus, urinary retention | No difference between groups | No difference between groups | No difference between groups |

VAS = visual analog scale.

^a Ascanio RS, Mahaney G, Sama MC, Soni AK, Oriol NE. A single dose of epidural morphine alleviates postpartum perineal pain for at least one week. *SOAP* 1997:A153.

^b Nunlee WY, Perry PM, Lawal AH, Ivankovich AD. Does a single dose of epidural morphine provide extended analgesia after vaginal delivery? *Anesthesiology* 2000:A160.

^c Jadad score consists of one point for describing the study as randomized, double blind, and adequate description of dropouts/withdrawals. Extra marks are awarded if the randomization schedule is described/appropriate and if blinding is described/appropriate.¹¹

occurred as a result of insufficient sample size or differing supplemental analgesic regimes.

The strengths of our study include the large sample size (other studies enrolled <125 patients) and stratification of parity to ensure adequate distribution in both groups. Our earlier work demonstrated that between postpartum Day 1 and Day 7, multiparous women experienced 10%–30% less perineal discomfort than that of primiparous women.¹ This discrepancy could potentially explain the lack of efficacy of 2-mg epidural morphine in the study of Nunlee et al.[†] In their study, there was an unequal distribution of primiparous patients in the morphine group (56%) compared with the control group (8%). Primiparous women who received epidural morphine had similar supplemental analgesic and pain scores compared with the multiparous women who received epidural saline. We demonstrated that women with varying degrees of perineal trauma still benefit from the use of epidural morphine; however, only 26% of our population had minor trauma. Five patients in the minor perineal trauma group ($n = 59$) required additional analgesics in the first 24 h postpartum; however, all of the patients were in the saline group. It remains to be confirmed by a further larger study whether patients with minor perineal trauma benefit as much as patients with more extensive trauma.

Our study would have been improved by evaluating functional activities of daily life, such as ability to sit and urinate in the first day. Qualitative assessment of the patient's perineal pain may have revealed further differences in the first day experiences. However, many patients delivered during evening and

nighttime hours and were discharged from the hospital within 24–48 h postpartum. Ensuring time available to question patients in the first 24 h postpartum can be challenging among those delivering vaginally. Maternal satisfaction did not seem to be different between the 2 groups; however, the tool used to assess satisfaction with analgesia was crude. Perhaps a multidimensional satisfaction scale or assessing satisfaction over a longer period of the postpartum recovery would have identified differences between the groups, if there were any.

Generalizing our findings to other labor and delivery populations requires a comment. Although only 446 women of 1110 approached agreed to participate in the study, the remaining 58% declined for reasons that would be unlikely to diminish the effect of epidural morphine, should it have been given. Women who declined to participate did so because of a concern over receiving additional medication, particularly an opioid. We do not have a biological reason why the epidural morphine would have worked less effectively in this group of nonparticipants. Our study also had a higher rate of operative vaginal delivery (32%) than the general Ontario delivery population, which has been estimated at 15%.¹² However, our study population is different than the general delivery population, in that they had selected epidural analgesia for labor. Whether causal or not, epidural analgesia has been associated with an increased risk of operative delivery. Other factors associated with increased incidence of an operative vaginal delivery were present in our study population including older age participants,

who were more likely to be primiparous and Caucasian.¹³ Our overall institutional cesarean delivery rate during the study period was approximately 34%. We await investigations by other labor and delivery units on this analgesic modality to make a final assessment of the generalizability of our study.

The use of epidural morphine in the postpartum period requires an increased period of maternal monitoring for potential respiratory depression. The incidence of respiratory depression with the use of epidural or intrathecal morphine is lower in obstetric patients compared with nonobstetric patients and has been estimated between 0.07% and 0.9%.¹⁴ Our current institutional practice requires monitoring of the mother's sedation level and respiratory rate for 24 h after epidural or intrathecal morphine administration. Other side effects of epidural or intrathecal morphine include pruritus, nausea and vomiting, and urinary retention. We may not have detected a difference because the incidence of all side effects has decreased with reduction of the epidural dose administered in the past 15 yr. Original administration of epidural morphine began with doses between 3 and 5 mg, and the incidence of pruritus was between 40% and 80% and nausea/vomiting between 20% and 60%.¹⁵ Although our study did not demonstrate an increased incidence of side effects, this is likely attributable to an inadequate sample size to assess for differences among infrequently occurring events. Further study is required to assess whether the analgesic-sparing effect of epidural morphine is worth any increased side-effect risk such as bladder catheterization or prolonged hospitalization secondary to urinary retention.

A new sustained-release morphine formulation of morphine has become available in the United States for postoperative analgesia.¹⁶ This product uses proprietary-protected lipid technology that surrounds conventional morphine sulfate, enabling a sustained release of morphine for up to 48 h. The reports on use of this drug have been limited to fewer than 200 patients after cesarean delivery; however, it seems to offer improvements after the first 12 h over conventional epidural morphine. This product has not been evaluated in postvaginal delivery patients and may be hindered by the requirement for monitoring side effects for 48 h after administration. Discharge from hospital often occurs for postvaginal delivery patients between 36 and 48 h postpartum.

As a result of our study findings, women at our institution who deliver vaginally now receive scheduled doses of acetaminophen and ibuprofen until

discharge, and women with epidural labor analgesia are offered a single dose of postpartum epidural morphine. We have implemented a standard order set for these patients with monitoring variables, side-effect treatment, and a link to obstetrician postpartum orders when the 24-h monitoring period ends. The ideal dose for postvaginal analgesia has yet to be evaluated, and the confirmation of these findings in populations with younger patients and fewer operative deliveries has yet to be examined.

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Transient Changes in Brain Tissue Oxygen in Response to Modifications of Cerebral Perfusion Pressure: An Observational Study

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BACKGROUND: The relative merits of the mechanisms for the maintenance of brain tissue oxygenation (PbtO₂) have been much debated. There is a wealth of studies regarding various factors that may determine the absolute value and changes in PbtO₂. However, only a few of them analyzed fast (few minutes) and transient behavior of PbtO₂ in response to variations (waves) of intracranial pressure (ICP) and cerebral perfusion pressure (CPP).

METHODS: This was a retrospective analysis and observational study. PbtO₂, arterial blood pressure (ABP), and ICP waveforms were digitally monitored in 23 head-injured patients, admitted to the Neuroscience Critical Care Unit, who were sedated, paralyzed, and ventilated. Computer recordings were retrospectively reviewed. The dynamic changes in PbtO₂ in response to transient changes in ABP and ICP were investigated.

RESULTS: Several patterns of response to short-lasting arterial hypotension and hypertension, intracranial hypertension, cerebral vasocycling, and cerebral hyperemia were observed and characterized. During the majority of the transient events, PbtO₂ generally followed the direction of changes in CPP. Only during episodes of hyperemia, CPP and PbtO₂ changed in the opposite direction. Changes in PbtO₂ were delayed after dynamic changes in ABP, CPP, and ICP. The CPP-PbtO₂ delay during changes provoked by variations in ABP was 35.0 s (range: maximum 827.0 s; minimum 0.0 s) compared with changes induced by variations in ICP of 0.0 s (range: maximum 265.0 s; minimum 0.0 s); the difference was significant at $P < 0.0001$.

CONCLUSIONS: PbtO₂ is more than a number; it is rather a waveform following rapid changes in ICP and ABP. We show that PbtO₂ generally tracks the direction of CPP irrespective of the state of cerebral autoregulation.

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Evaluation of brain tissue oxygen (PbtO₂) is gaining momentum in the management of critically ill patients based on the assumption that tissue brain hypoxia leads to brain damage and is related to poor outcome.¹ PbtO₂

is the partial pressure of oxygen measured in the extracellular fluid of the brain. It is the product of oxygen delivery and washout with cerebral blood flow (CBF), oxygen diffusivity, and cerebral metabolism.² In neurointensive care, PbtO₂ is usually monitored along with other physiological modalities including arterial blood pressure (ABP) and intracranial pressure (ICP).^{3,4}

We reviewed brain tissue oxygen studies devoted to the static relationship between cerebral perfusion pressure (CPP) and PbtO₂⁵ during long-duration monitoring. "Static relationship" refers to PbtO₂ measured over a long period at different stable levels of CPP. We focused our study on short-duration instead of long-duration intervals. Evaluating the tracing in short-duration intervals (within 30-min periods), we could detect several rapid modifications in ABP, ICP, PbtO₂, and CPP, which

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MC, IT, AL, MJ, PH, AG, JDP, and PS helped in manuscript preparation. DKR and MC helped to conduct the study, MC in design of the study, DJK in data collection, and PS in the analysis of data.

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might be caused either by external stimulations or spontaneous cardiovascular and dysautonomic disorders. We call these interrelationships “dynamic.” In particular, rapid changes in PbtO₂ correlated with changes in CPP have shown promise to contribute to a better understanding of CPP management of patients with traumatic brain injury.^{6,7}

The aim of our retrospective observational study was to describe and analyze the dynamic changes in PbtO₂ that could be related to transient changes in CPP initiated by variations of ABP or ICP. We have classified these changes into groups defined according to precipitating factors and patterns of behavior. An important overall caveat to this study is that we evaluated the impact of transient changes in CPP, ICP, and ABP on changes in PbtO₂; we did not evaluate all events that might influence PbtO₂, such as arterial saturation, Paco₂, venous outflow, and variables of mechanical ventilation.

METHODS

In Addenbrooke’s Hospital, all brain modalities were monitored and recorded as part of standard clinical care after head injury. Our local ethical committee approved brain monitoring in all recruited patients. Individual consents were obtained from next of kin.

Patients

Of 170 severely head-injured patients with ICP/ CPP brain monitoring admitted to the Neuroscience Critical Care Unit of Addenbrooke’s Hospital in Cambridge, United Kingdom, between 2003 and 2006, we retrospectively selected those in whom brain tissue oxygenation was measured continuously. We have retrospectively studied 325 events of rapid changes of PbtO₂ in 23 head-injured patients. All patients were sedated, their lungs mechanically ventilated, and managed according to the “ICP/ CPP oriented protocol for head injury,”⁸ whereby we attempted to maintain ICP <20 mm Hg and CPP >70 mm Hg. Drainage of cerebrospinal fluid (where possible), mannitol or hypertonic saline administration, hyperventilation, and the use of central nervous system depressants (typically barbiturates) have all been used to reduce ICP.

CPP maintenance involved the use of adequate preload expansion, inotropes, and vasopressors. Initial baseline monitoring and therapy were applied to all patients, and refractory problems were managed by therapy escalation, with the choice of intervention determined by clinical presentation and physiological monitoring. Mechanical ventilation was set to achieve a Paco₂ of 4.5–5.0 kPa and a Pao₂ of 13–15 kPa. Fio₂ and Spo₂ were not monitored continuously (respirators used did not export these data).

Methods of Measurement

PbtO₂ was monitored using the Neurotrend multiparameter sensor (Codman, Johnson & Johnson, Raynham,

MA).⁹ The probes were inserted into the brain parenchyma in the right frontal area, regardless of the side of the lesion, through a cranial access device (Technicam, Newton Abbot, UK) or through a craniotomy intraoperatively. They were positioned approximately 2.5 cm below the dura. The volume of brain tissue for measuring PbtO₂ in the literature is 3 mm³.^{4,6,10} ABP was monitored invasively using a standard pressure monitoring kit (Baxter Healthcare Corp. CardioVascular Group, Irvine, CA). ICP was monitored using an intraparenchymal probe (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA). All signals were digitized using an A/D converter (DT9801, Data Translation, Marlboro, MA), sampled at a frequency of 50 Hz, and recorded using a laptop PC with ICM+ software (Cambridge, UK, www.neurosurg.cam.ac.uk/icmplus). The same software was later used for retrospective analysis of stored signal samples.

Data Analysis

Sampled signals of ICP, ABP, and PbtO₂ were first subjected to manual artifact detection and removal to isolate true events. Artifacts are generally of 4 types. Fast bimodal variations (more than ±20 mm Hg from baseline) were extracted as they most frequently are associated with periods of tracheal suction. Periods of absent ABP pulse waveform were associated with events of arterial line flushing. Periods (longer) of zero dynamics of all signals were associated with malfunction of transducers. Fast changes in PbtO₂ not associated with changes in ABP and ICP were also omitted, because these events could not be interpreted within the scope of our initial aims. After exclusion of these artifacts, we presumed that variables such as Paco₂, Fio₂, Pao₂, and temperature were reasonably stable during the analyzed episodes. We did not include deliberate interventions, such as physiotherapy and tracheal suction, transient effects of introduction or change of rate of vasoactive drugs, or boluses of mannitol or hypertonic saline.

Next, second-by-second time trends of mean ICP, ABP, CPP, and PbtO₂ were created to study changes in PbtO₂ related to changes in ABP and ICP. CPP was calculated as the difference between mean ABP and ICP. The data were further smoothed with a 30-s moving average filter to remove the cardiac and respiratory components. We then observed the monitor tracing and considered transient events. A “transient event” was defined as a short-duration change (within 30-min periods; Table 1) in PbtO₂, ICP, and ABP of a magnitude clearly visually greater (differences at least approximately 0.8 kPa for PbtO₂, approximately 20 mm Hg for ABP, CPP, and approximately 10 mm Hg for ICP) than the background “noise” variations on the tracing. We divided the PbtO₂ events into 2 groups, depending on whether ABP (ABP-led events) or ICP (ICP-led events) was the first variable to change. The ABP-led events were

Table 1. Summary of Physiological Data During the Different Transient Events Observed

| | ABP min (mm Hg) | ABP max (mm Hg) | ABP amp (mm Hg) | ABP length (s) |
|---------|-----------------------------|-----------------------------|-----------------------------|------------------------------|
| Median | 87.9 | 104.8 | 17.7 | 254.5 |
| Minimum | 1.0 | 1.8 | 0.7 | 21.0 |
| Maximum | 131.9 | 167.7 | 124.8 | 1404.0 |
| | CPP min (mm Hg) | CPP max (mm Hg) | CPP amp (mm Hg) | CPP length (s) |
| Median | 68.5 | 88.6 | 18.9 | 259.2 |
| Minimum | 10.1 | 47.7 | 2.2 | 21.0 |
| Maximum | 106.4 | 137.5 | 105.5 | 1404.0 |
| | ICP min (mm Hg) | ICP max (mm Hg) | ICP amp (mm Hg) | ICP length (s) |
| Median | 14.3 | 21.2 | 7.2 | 274.0 |
| Minimum | -0.8 | -0.0 | 0.1 | 21.0 |
| Maximum | 56.6 | 81.1 | 52.3 | 1949.0 |
| | PbtO ₂ min (kPa) | PbtO ₂ max (kPa) | PbtO ₂ amp (kPa) | PbtO ₂ length (s) |
| Median | 2.1 | 2.78 | 0.8 | 318.0 |
| Minimum | 0.0 | 0.1 | 0.0 | 33.0 |
| Maximum | 7.8 | 9.2 | 5.5 | 1923.0 |

Data are presented as median and its range.

ABP = arterial blood pressure; CPP = cerebral perfusion pressure; ICP = intracranial pressure; PbtO₂ = brain tissue oxygen; min = minimal value during the event; max = maximal value during the event; amp = magnitude of changes; length = duration of the event.

further subdivided based on whether cerebrovascular autoregulation was intact or impaired. In general, with intact cerebrovascular reactivity, cerebral blood vessel diameters respond to a decrease or increase in ABP to maintain CBF at a constant level. This in turn provokes a secondary increase or decrease in ICP because of a respective increase or reduction in cerebral blood volume.^{11,12} Therefore, when autoregulation is intact, ABP and ICP change in opposite directions. With impaired cerebrovascular reactivity, ICP passively follows changes in ABP both during hypotension and during hypertension.¹³ Separation between intact cerebrovascular reactivity and impaired reactivity was defined by evaluating the ABP-ICP correlation on the monitor tracing. We considered a negative correlation to be an indicator of good autoregulation and a positive correlation to indicate impaired autoregulation. Considering that some transient events we analyzed lasted <1 min, the pressure-reactivity index¹⁴ could not be used for assessment of autoregulation because it is calculated from an average period of 300 s. Within ICP-led events, changes in PbtO₂ during ICP vasogenic waves were studied. Vasogenic waves occur as a result of self-sustained vasodilatation of the regulating vessels in the cerebral circulation leading to increased cerebral blood volume and ICP.¹⁵ These include isolated increases in ICP (sudden increase in ICP lasting <5 min with variable intensity) and plateau waves (sudden rapid increase of ICP to 50–100 mm Hg for 5–20 min).^{16,17}

The captured data covered a period of 3 h to 10 days per patient.

Statistical Analysis

The nonparametric Mann-Whitney *U*-test was used. The data were previously tested using the

Kolmogorov-Smirnov test and not found to be normally distributed. The Mann-Whitney *U*-test was therefore used for comparisons. The analysis was performed by using commercial software (STATISTICA 6.0, StatSoft, Tulsa, OK). All data indicated were expressed as median values and their range.

RESULTS

The minimum and maximum values, the length and the amplitude of ABP, CPP, ICP, and PbtO₂ during the events we observed are summarized in Table 1.

Examples of rapid changes in PbtO₂ are presented in Figures 2–7 as individual observations of events in individual patients. They were chosen to indicate changes in PbtO₂ in response to change in CPP according to the criteria of “most spectacular” representation of the underlying hemodynamic phenomenon. This is consistent with the type of our review as “observational study.”

ABP-Led Events in Patients with Intact Cerebral Autoregulation (Negative ABP-ICP Correlation; *n* = 179)

In patients with preserved autoregulation, sudden hypotension (Fig. 1A) consistently provoked a temporary increase in ICP because of compensatory vasodilatation, and a decrease in PbtO₂. The PbtO₂ responses were delayed with respect to the onset of ABP and CPP (30.0 s; range, 0.0–827 s) and ICP (25.0 s; range, 0.0–827 s). These delays did not differ significantly. During hypertensive events (Fig. 1B), there was a decrease in ICP (because of compensatory vasoconstriction) and an increase in PbtO₂ with a delay of 40.0 s (range, 0.0–380 s) with respect to ABP and CPP and 36.0 s (range, 0.0–380 s) with respect to ICP; differences between delays were nonsignificant.

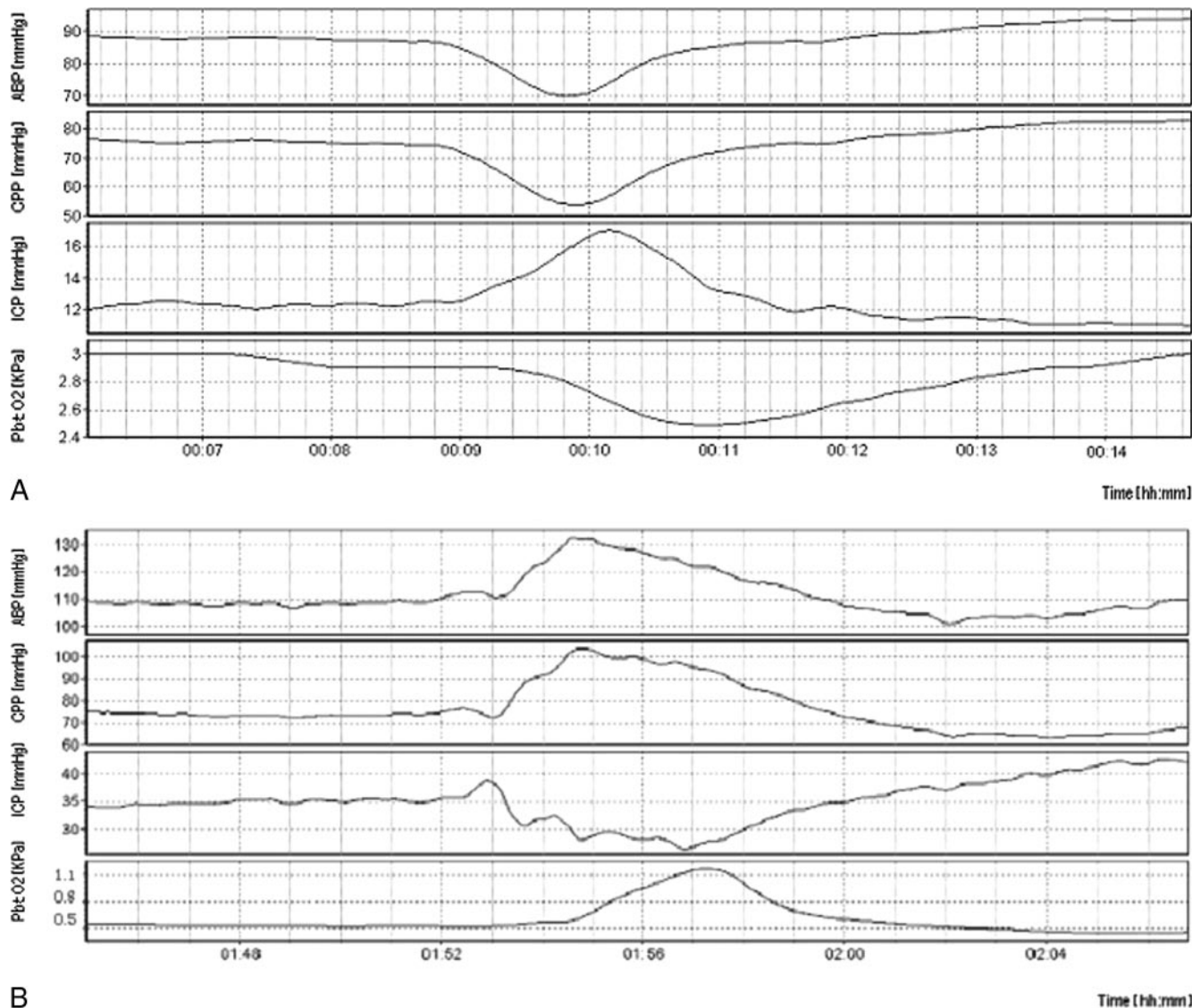


Figure 1. Hemodynamic events with cerebrovascular reactivity preserved. Rapid changes in arterial blood pressure (ABP) were accompanied by intracranial pressure (ICP) modification moving in the opposite direction. Cerebral perfusion pressure (CPP) followed changes in ABP. Brain tissue oxygen (PbtO₂) generally followed the CPP trend with a delay relative to the other variables. A, Hypotensive event; B, hypertensive event.

ABP-Led Events in Patients with Impaired Cerebrovascular Autoregulation (Positive ABP-ICP Correlation; *n* = 76)

During hemodynamic events occurring in the state of disturbed cerebrovascular reactivity, ICP generally followed the direction of ABP changes (Fig. 2A and B), without any significant delay as did PbtO₂ but with a delay of 41.0 s (range, 0.0–325 s) with respect to ABP and CPP. The delay between ICP and PbtO₂ change was 39.0 s (range, 0.0–325 s). No significant (*P* > 0.05) difference was found in the delay of PbtO₂ changes between hypotensive or hypertensive events. The duration of the transient changes in ABP, CPP, and ICP was significantly (*P* < 0.05) longer with autoregulation intact. ABP events lasted for a median of 291.0 s (range, 33.0–1079.0 s), CPP events 292.0 s (range, 33.0–1079.0 s), and ICP events 313.0 s (range, 44.0–1079.0). In contrast, for events with impaired autoregulation, ABP transients lasted 191.0 s (range,

21.0–1201.0 s), CPP lasted 191.0 s (range, 21.0–1037.0 s), and ICP lasted 190.0 s (range, 21.0–1047 s). No difference was found in the duration of PbtO₂ waves.

ICP-Led Events: PbtO₂ Behavior in Response to ICP Changes (*n* = 61)

Plateau waves (Fig. 3) and isolated gradual increases in ICP (Fig. 4) caused CPP to decrease, which was followed by a decrease in PbtO₂. A change in PbtO₂ did not show any significant delay with respect to ICP and CPP. We also observed fluctuations of PbtO₂ during ICP B waves (Fig. 5). However, cross-spectral analysis did not provide any evidence of correlated behavior between the 2. Finally, 2 events in this group followed a pattern that could be described as hyperemia¹⁸ (Fig. 6). During the events, a disproportionate increase in ICP was accompanied by a mild

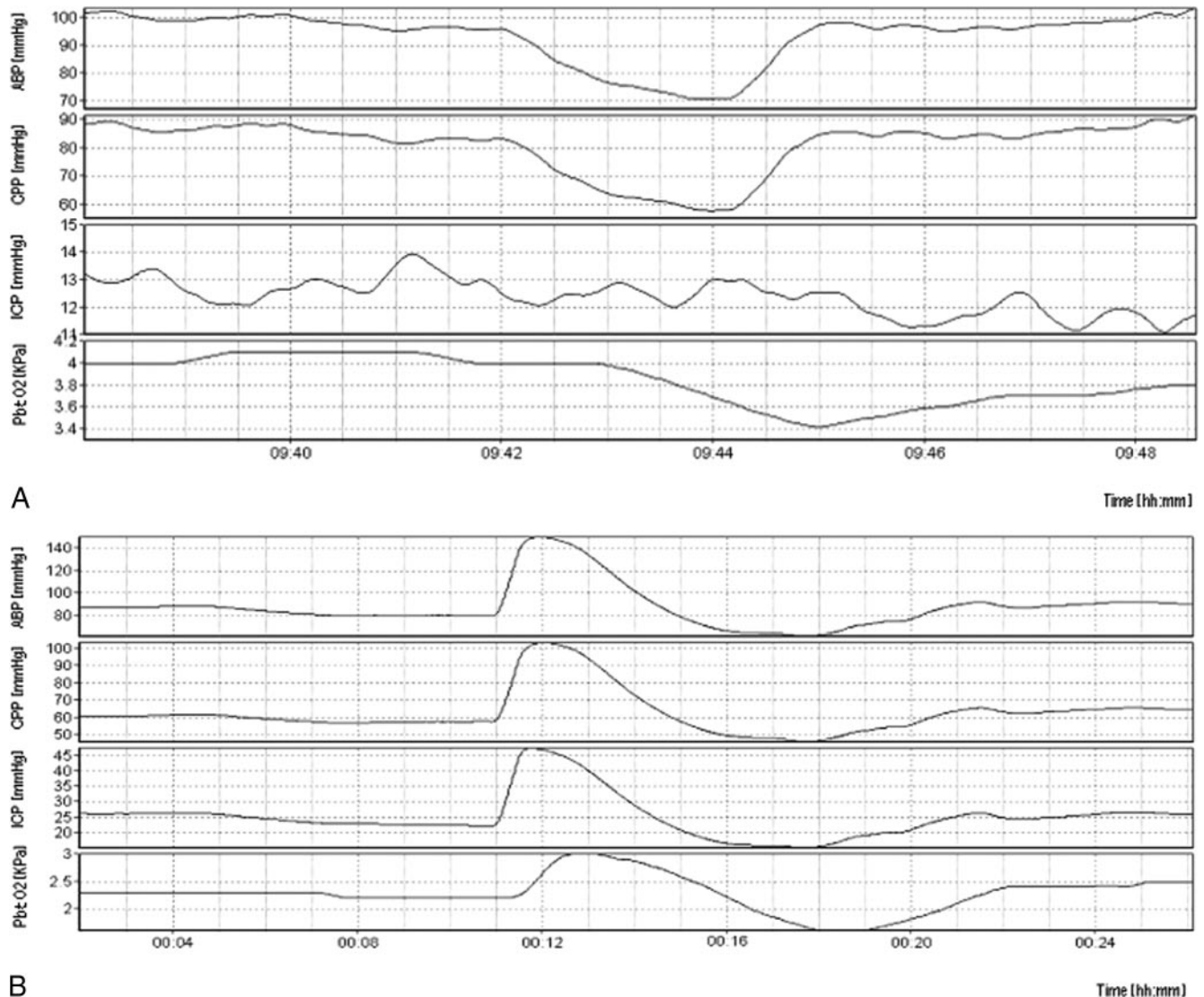


Figure 2. Hemodynamic events with impaired cerebrovascular reactivity. Sudden arterial blood pressure (ABP) changes accompanied by a passive behavior in intracranial pressure (ICP). Cerebral perfusion pressure (CPP) followed ABP. Brain tissue oxygen (PbtO₂) always follows the direction of CPP with a delay. A, Hypotensive event; B, hypertensive event.

increase in ABP, resulting in a decrease in CPP and an increase in PbtO₂.

Comparison Between ABP-Led and ICP-Led Events

In our group of patients and recording, events triggered by sudden changes in ABP were more frequent than ICP-driven events (81% vs 19%). CPP-PbtO₂ and ICP-PbtO₂ interbehavior had a significant delay in ABP-led events, which was absent in ICP-led events where the parameters' modifications occurred almost simultaneously.

DISCUSSION

Transient changes were observed in PbtO₂ related to dynamic changes in ABP or ICP. In general, PbtO₂ followed the direction of CPP. The only exception was a presumed hyperemic event when CPP and PbtO₂ changed in the opposite direction.

Changes in PbtO₂ were present in all cases regardless of the state of autoregulation or the origin of the event (hemodynamic or ICP-related).

During hemodynamic events, PbtO₂ is generally not expected to change during periods of good autoregulation, when CBF is supposed to remain constant. Despite that, changes in PbtO₂ were observed, which could mean that activation of the vascular response is not immediate, leading to temporary changes in CBF and, consequently, fluctuations in PbtO₂.¹⁹ Although we observed that changes in PbtO₂ may occur regardless of the integrity of autoregulation, we would expect the extent of PbtO₂ changes to be smaller with intact autoregulation. However, this was not demonstrated in our study because we did not find any significant difference in amplitude of PbtO₂ changes (difference between the maximum and the minimum value of PbtO₂ during the event) between events with autoregulation intact or impaired. Disparity between

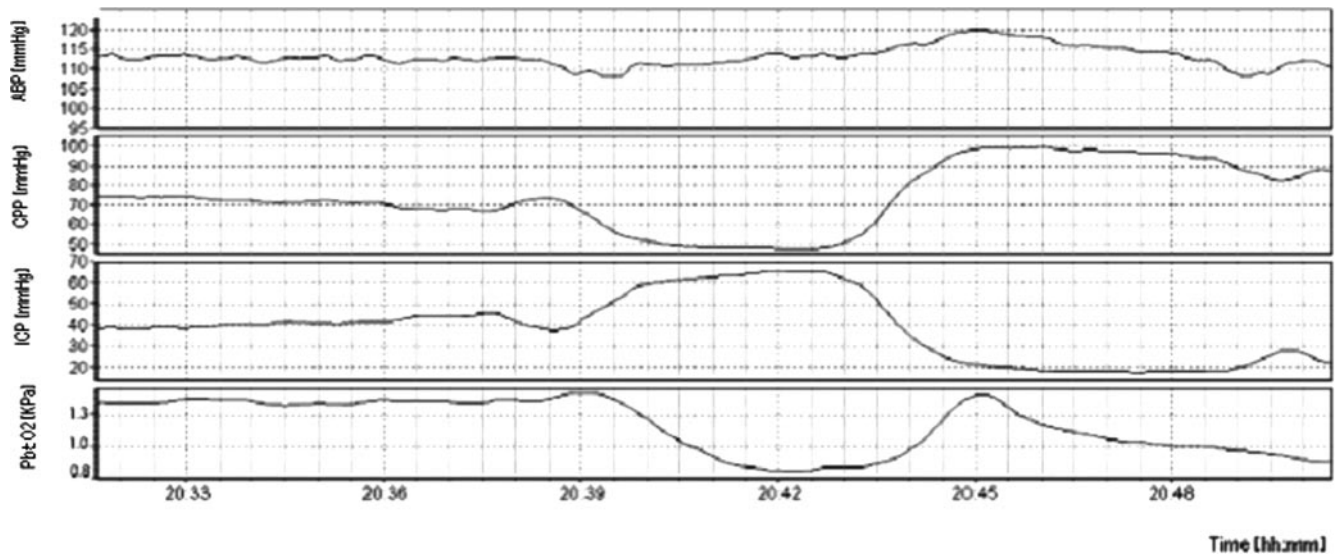


Figure 3. Plateau wave of intracranial pressure (ICP). After an ICP increase, almost instantaneous reduction in brain tissue oxygen (P_{btO_2}) was noted that mirrored the ICP. Arterial blood pressure (ABP) did not change and cerebral perfusion pressure (CPP) decreased during a wave.

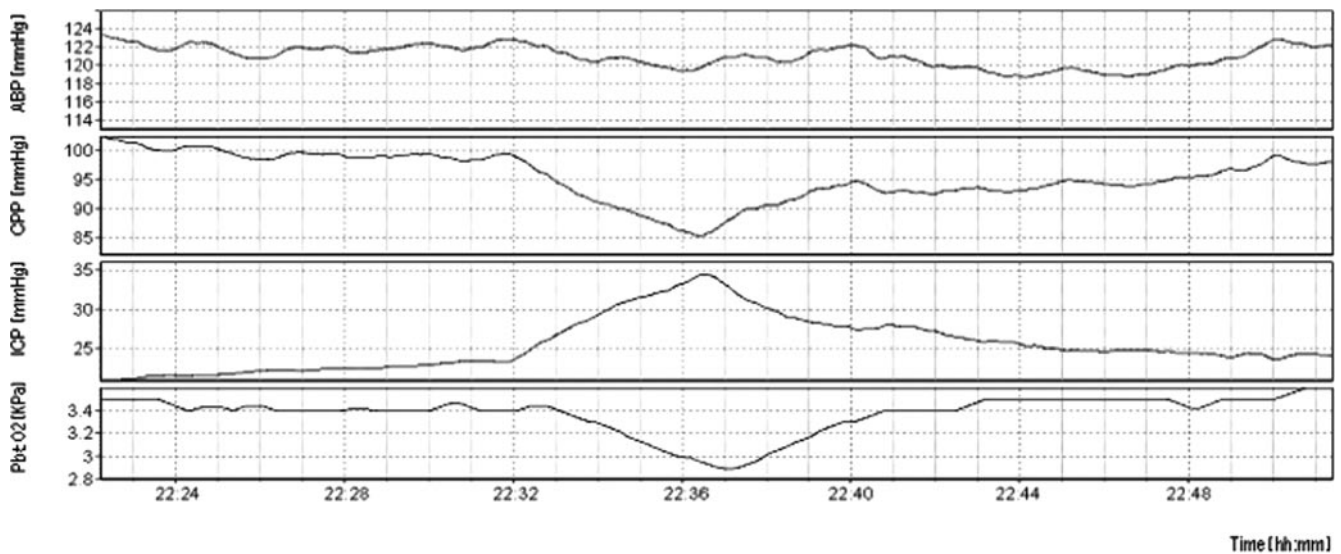


Figure 4. Isolated gradual increase in intracranial pressure (ICP). ICP increased gradually, arterial blood pressure (ABP) remained relatively stable, and cerebral perfusion pressure (CPP) decreased. Brain tissue oxygen (P_{btO_2}) followed almost instantly the change in ICP.

autoregulation and variability of P_{btO_2} may be caused by CPP-related changes in oxygen diffusibility, leading to fluctuation in the capillary-tissue gradient not related to changes in CBF.²⁰

During the ICP-led events, such as plateau wave, P_{btO_2} decreases despite the hypothetical increase in oxygen delivery caused by vasodilatation. P_{btO_2} usually changed with a delay relative to ABP, ICP, and CPP. The factors responsible for such a delay might have been the oxygen sensor's characteristics, blood vessel distribution into the parenchyma and its characteristics,²¹ and the delay in reactivity of the vessels. The probe's location, whether it was placed in normal brain or in pericontusional areas, could have influenced the delay as well.²² Indeed, P_{btO_2} may depend on local tissue angioarchitecture; therefore, the dominance of

arterial or venous vessels in the immediate proximity of the P_{btO_2} sensor may lead to coupling between P_{btO_2} -CBF or P_{btO_2} -OEF ($AVDO_2$), respectively, where OEF = oxygen extraction fraction.²³ The probe used in this study had a response time of approximately 15 s (information obtained from the manufacturer) and so was capable of monitoring P_{btO_2} dynamics with relatively high temporal resolution.

To evaluate and compare the P_{btO_2} delays in the ABP-led and ICP-led events, we used the CPP time trend to define the onset of the events. Our assumption was that CPP is the most important factor affecting CBF and consequently P_{btO_2} both in ICP- and ABP-led events. In general, the delay between CPP and P_{btO_2} can be interpreted according to the principles involved in tissue gas diffusion, depending on

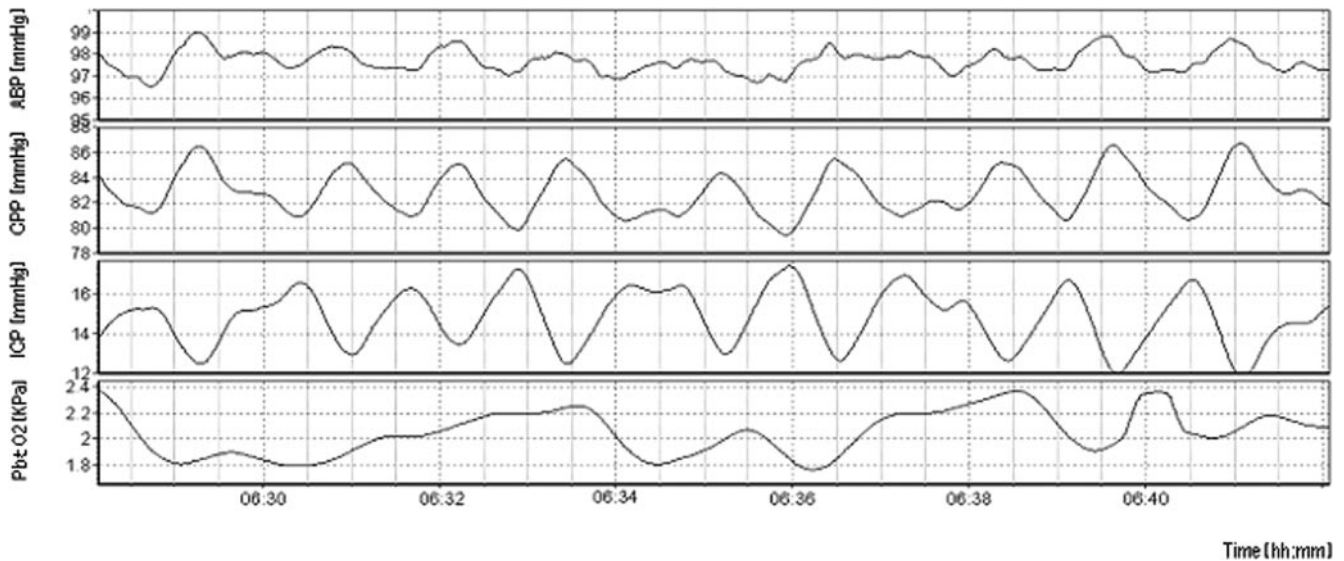


Figure 5. B waves. Rapid spontaneous oscillations in intracranial pressure (ICP) and arterial blood pressure (ABP) in opposite directions. Fluctuations in brain tissue oxygen (PbtO₂) were observed, which appeared to be unsynchronized (slower) with a source of vasocycling.

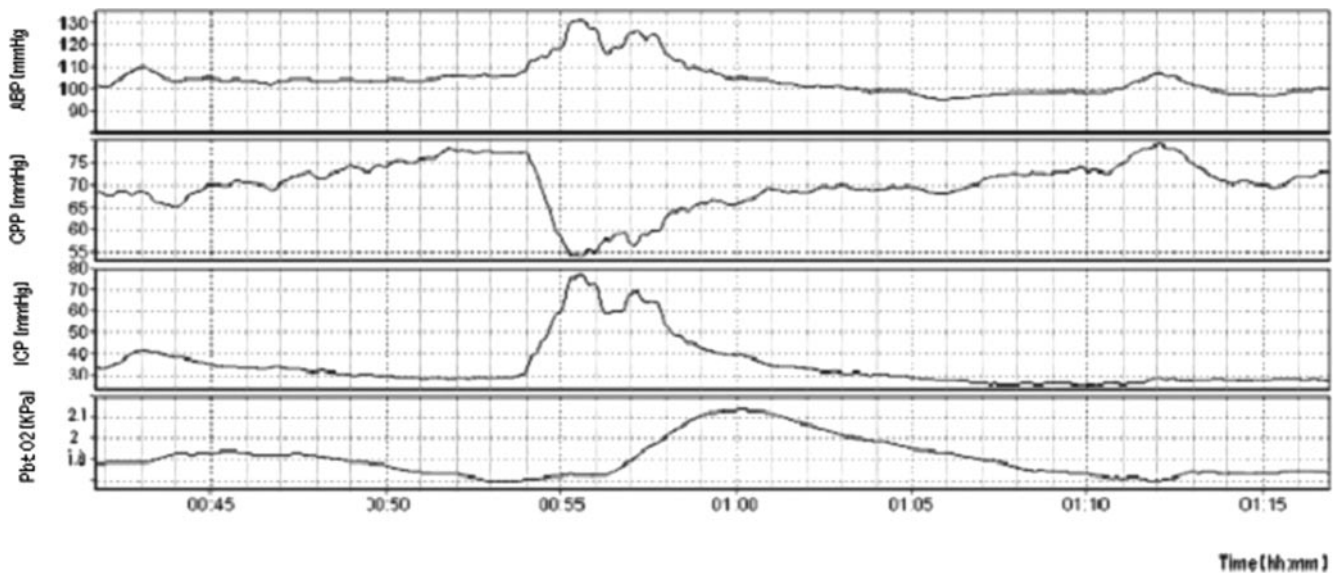


Figure 6. Hyperemia. Intracranial pressure (ICP) and arterial blood pressure (ABP) were increased almost simultaneously. This was the only case when brain tissue oxygen (PbtO₂) changed in the opposite direction from cerebral perfusion pressure (CPP).

gas partial pressure, the membrane's surface and thickness, blood perfusion, and time of contact of the blood with the tissue. Nevertheless, in our study concerning very short-term events, blood perfusion may be the most determinant factor influencing oxygen diffusion time. We have assumed that, because of the short duration of these events (from 20 s to a maximum of 30 min), the metabolic effects on PbtO₂ were irrelevant in sedated and paralyzed patients. Validity of this assumption was also demonstrated in the study by Masamoto et al.,²¹ which found that the cerebral metabolic rate for O₂ has a relatively small impact on PbtO₂ changes compared with the effect of rapid variations in local CBF in short-term events.

Our results show that a CPP-PbtO₂ delay is not significant in the events characterized by primary ICP modification compared with ABP-led events, regardless of the state of autoregulation. This could stem from the fact that during ABP-led events CPP was influenced both by ABP and ICP changes, whereas in ICP-led events it only reflected ICP modifications. Therefore, in the first instance, changes in CPP result from an interaction between 2 variables with different temporal characteristics, whereas in the latter, they are only determined by modifications in ICP. Subsequently, for extracranial events (ABP changes), it seems to take longer to affect cerebral circulation than events originating in the brain (e.g., cerebral vasodilatation).²⁴

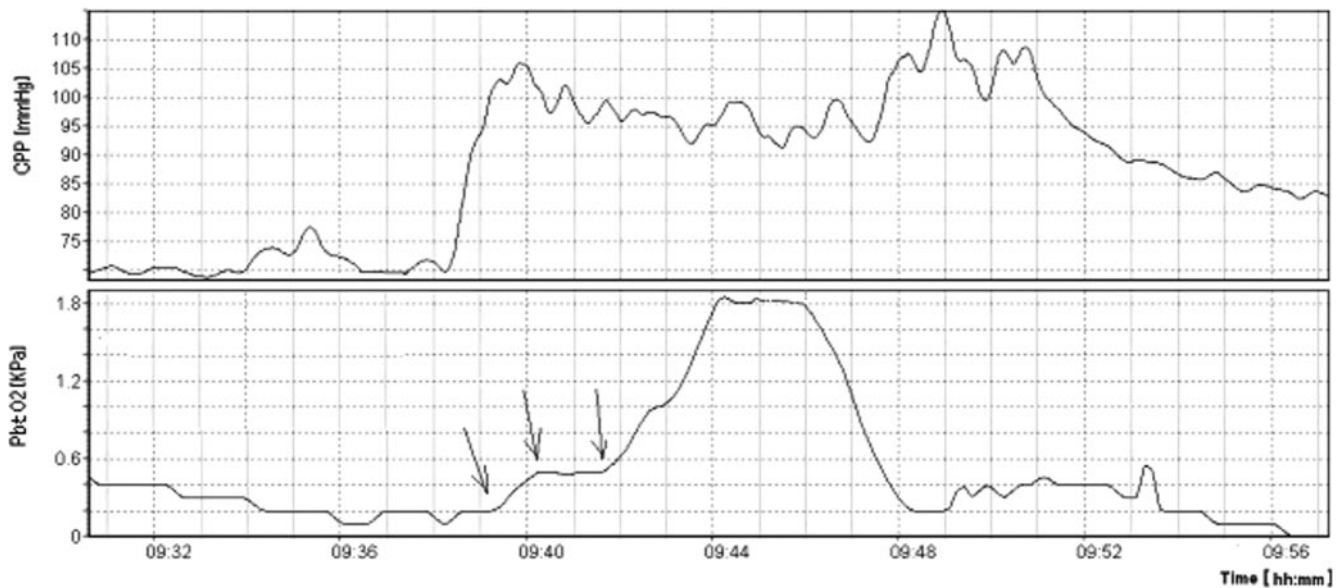


Figure 7. Evaluation of the delay between cerebral perfusion pressure (CPP) and brain tissue oxygen (PbtO₂). Illustration of difficulty in precise identification of the onset of the event. Arrows point to possible onset times. A decrease in PbtO₂ to 0 kPa seen at the end of this fragment is probably caused by 0 drift of the tissue oxygenation probe.

B waves, which consist of relatively rapid and repetitive oscillations in ICP (periods of 20 s to 1 min), not necessarily accompanied by similar oscillations in ABP, are not usually reflected directly in the PbtO₂. Instead, independent but slower PbtO₂ fluctuations may be observed. We can speculate that this is because ICP increases and decreases quickly in a matter of seconds and not minutes as in the other ICP events and therefore does not reach values high enough to provoke a regular pattern.

In our results, ABP was more susceptible to changes than ICP. We speculate it was due to the several mechanisms involved in ABP regulation such as sympathetic and parasympathetic systems and baroreceptor reflex. All of these are responsible for continuous hemodynamic variability. The cerebrospinal fluid circulation lacks these regulation systems so that it less often modifies.

Our study was observational, but its direct clinical usefulness is uncertain. Nevertheless, we found that PbtO₂ is more than the number; rather, it is a waveform and information included in its dynamics should be interpreted in conjunction with continuous monitoring of CPP and its components. Another “practical” conclusion might be connected to interpretation of the “oxygen reactivity index.”⁷ The oxygen reactivity index is constantly positive and at high CPPs may, at most, decrease to zero, which may not necessarily indicate “good autoregulation” but instead state of excessive CPP, which leads to hyperemia.

There were some limitations to our study. The precise location of the probe and whether it was in the normal or pericontusional brain tissue was not considered in this study. Despite that, we found a consistent pattern of behavior in all patients. Our intention was to analyze changes in time among ABP, PbtO₂,

and ICP, rather than the magnitude of these changes. The magnitude may be affected by the location, but it is unlikely that the time profile is affected. The location of the probe was determined by a triple-lumen cranial access device.²⁵ Of course, a clarification of probe location will give more information and data to be analyzed in further prospective studies. We understand that interpretation of local measurements by comparing them with global variables (such as CPP) may be misleading.

Unfortunately, we were not able to identify whether the modifications in ABP or ICP occurred spontaneously or by extrinsic triggers. Whichever was the cause leading to an event, it should affect only the duration of the event but not the respective behavior between the variables considered. We focused on the timepoint immediately after the onset of changes to determine the sequence of intermodifications.

Visual inspection of the onset of changes in the variables studied as well as a cross-correlation approach yielded delayed measurements, causing an uncertainty of several seconds (Fig. 7). However, this order of error was still relatively small compared with the delays and differences detected and therefore did not undermine the validity of our findings of the existence of the delay and of the significant differences between the groups.

Another limitation of our study was that we did not consider arterial blood oxygen (Pao₂) and arterial carbon dioxide (Paco₂). They could have explained the etiology of the observed PbtO₂ modifications. However, we analyzed only these “transients” of PbtO₂ which, to the best of our knowledge, were not associated with changes in ventilation variables; tracheal suction episodes were filtered out, and changes

of Fro_2 were also excluded (patients' notes and continuous recordings of respiratory rate using spectral analysis of ICP waveform). Data were also free from major desaturation episodes related to other temporary problems with mechanical ventilation.

We conclude that PbtO_2 monitoring needs to be viewed not just as a static value but also as a tool for examining and understanding the temporal character of physiopathological mechanisms underlying modifications of other intracranial variables. We showed that PbtO_2 generally tracks the direction of CPP and does not seem to be influenced by the state of cerebral autoregulation. The exception was hyperemic events when PbtO_2 and CPP changed in opposite directions. Our findings might be helpful for planning different therapeutic management. However, with the complexity of PbtO_2 , we would need to know the global oxygenation of the brain, instead of a small section of it, to be absolutely conclusive.

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The Brain Is a Source of S100B Increase During Endotoxemia in the Pig

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BACKGROUND: Cerebral dysfunction frequently complicates septic shock. A marker of cerebral dysfunction could be of significant value in managing sedated septic patients. Plasma S100 (S100B) proteins increase in sepsis. S100B is present not only in the brain but also in other tissues. The source of this protein has not been investigated in sepsis. Our aim in this study was to determine whether the brain is an important source of S100B in an experimental sepsis model.

METHODS: Twenty-seven pigs were anesthetized and randomized to either infusion of endotoxin at the rate of $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ($n = 19$) or saline ($n = 8$). Catheters were inserted into a cervical artery and the superior sagittal sinus. Blood samples were collected from both sites and physiologic data were registered before the start of the endotoxin infusion and hourly during the experiment. After 6 h, the animals were killed and brain tissue samples were taken from the left hemisphere. S100B in plasma was measured by enzyme-linked immunosorbent assay. Brain tissue samples were stained with biotinylated S100B antibodies.

RESULTS: In the endotoxemic animals, the arterial S100B concentration increased to 442 ± 33 and 421 ± 24 ng/L at 1 and 2 h, respectively, vs 306 ± 28 and 261 ± 25 ng/L in controls ($P = 0.018$ and 0.00053 , respectively). Mean superior sagittal sinus S100B concentrations were higher than mean arterial concentrations at all time points in the endotoxemic animals; however, significance was only reached at 2 h ($P = 0.033$). The focal glial S100B expression was more intense in the endotoxemic pigs than in controls ($P = 0.0047$).

CONCLUSIONS: Our results support the hypothesis that the brain is an important source of S100B in endotoxemia even though there may be other sources. These findings make S100B a candidate as a marker of cerebral dysfunction in septic shock.

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Despite advances in modern health care, severe sepsis and septic shock are still associated with a high mortality rate.¹ Furthermore, septic conditions are frequently accompanied by cerebral dysfunction, where the severity of brain dysfunction correlates with fatal outcome.² The pathophysiology of septic encephalopathy is not fully understood, but disruption of the blood-brain barrier (BBB),³ formation of

edema,⁴ decreased cerebral blood flow, and ischemia^{5,6} may all contribute to the effects on the central nervous system.⁷

A diagnostic and prognostic marker of cerebral dysfunction would contribute to our understanding of septic encephalopathy and may be of further value in therapeutic decisions, especially in sedated intensive care patients.

One of the candidate proteins proposed to serve as a marker of cerebral dysfunction is S100, a member of the calmodulin/parvalbumin/troponin C superfamily of calcium-binding proteins. S100 proteins are generally thought to be neuronal calcium sensor proteins that modulate biological activity via calcium binding.⁸ At least 20 S100 monomers have been identified.^{9,10} These S100 proteins exist mostly as dimers within the cell and are expressed in a cell-specific manner. The monomers S100A1 and S100B show a high degree of homology and are found as homodimers (BB) and heterodimers (A1B) in the cytoplasm of glial cells in the central nervous system.¹¹ Under physiologic conditions, they are also expressed in other cells, e.g., adipocytes, Schwann cells, melanocytes, and chondrocytes.¹² Moreover, S100A1B and S100BB are expressed in melanoma, glioma, and other solid tumors.¹³ A key

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step in the release of S100B from the central nervous system is the disintegration of the BBB,^{14,15} either as a general process by increased permeability or by focal brain tissue damage. S100B has been used to evaluate patients with brain damage from traumatic head injury, perinatal asphyxia, cardiac arrest, cardiac surgery, and stroke.^{16–20} Additionally, S100B has been shown to predict long-term outcome after cardiac arrest.²¹

Several studies have evaluated the connection between S100B levels and systemic infections without clarifying their role in clinical practice.^{22–25} It is not clear whether the brain is actually involved in the release of S100B in sepsis. One experimental study showed increased plasma S100B levels in endotoxemic pigs; however, the origin of S100B release was not investigated.²⁶

Because the pig is a widely used experimental animal model for studies of Gram-negative sepsis and S100B has been measured in these animals,^{27–30} we designed a controlled study to investigate the effect of endotoxin on plasma S100B levels and to determine whether the brain is the origin of this protein in plasma.

Our hypothesis was that the brain is the main source of plasma S100B in endotoxemia. The primary end point was to determine whether S100B is higher in sinus blood than in arterial levels in endotoxemia. A secondary end point was to investigate with immunohistochemistry whether the pattern of distribution or the intensity of S100B expression in brain tissue is altered in endotoxemic pigs as compared with nonendotoxemic controls.

METHODS

Animals

The study included 27 domestic breed pigs of both genders weighing between 23 and 31 kg (27 ± 0.4 kg, mean \pm SD). All animals were from 9 to 11 wk old and apparently healthy. All pigs were handled according to the guidelines of the Swedish National Board for Laboratory Animals and the European Convention on Animal Care. The experiment was approved by the Animal Ethics Committee of Uppsala University, Sweden.

Inclusion Criteria

The following inclusion criteria were applied: no apparent diseases, arterial oxygen tension (P_{aO_2}) >10 kPa, and a mean pulmonary arterial pressure of ≤ 20 mm Hg at baseline, which was 30 min after the completed preparatory procedure (see below).

Anesthesia

The animals had free access to water *ad libitum* until they were transported to the laboratory. To decrease the stress level before the induction of anesthesia, a single IM injection of 50 mg xylazine (Bayer, Leverkusen, Germany) was given to all animals as

premedication before transport to the laboratory. General anesthesia was induced by injecting a mixture of 6 mg/kg tilétamin-zolazepam (Zoletil forte vetTM, Virbac Laboratories, Carros, France), 2.2 mg/kg xylazine, and 0.04 mg/kg atropine (NM Pharma, Stockholm, Sweden) IM. Anesthesia was maintained with sodium pentobarbital ($8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; Apoteket, Umeå, Sweden), pancuronium bromide ($0.26 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; Organon, Oss, The Netherlands), and morphine ($0.48 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; Pfizer, Sollentuna, Sweden) dissolved in 2.5% glucose solution given as a continuous infusion. Sodium chloride infusion was administered, resulting in a total fluid administration rate of $30 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

Preparatory Procedure

A bolus dose of 20 mg morphine and 100 mg ketamine hydrochloride (Pfizer) was administered IV before securing the airway with a tracheotomy. The animals' lungs were mechanically ventilated throughout the experimental procedure (Servo 900CTM, Siemens-Elema, Stockholm, Sweden) with 30% oxygen in medical air. After completion of the preparation procedure, ventilation was adjusted to yield a P_{aCO_2} between 5.0 and 5.5 kPa, and respirator settings were then kept constant throughout the experiment. The respiratory rate was 25/min and the inspiratory-expiratory ratio was 1:2. The pigs were placed into prone position as soon as the preparation was completed, and a positive end-expiratory pressure of 5 cm H₂O was maintained to counteract atelectasis development.

A cervical artery was catheterized for pressure monitoring and blood sampling. A central venous line and a Swan-Ganz catheter were inserted through the internal jugular vein into the superior caval vein and into the pulmonary artery, respectively.

After a skin incision, 3 burr holes were placed around a superior sagittal suture behind the coronal sinus. The bone was carefully lifted off the dura mater in a small area enabling the visualization and cannulation of the superior sagittal sinus. A 2.1F cannula was inserted into the superior sagittal sinus.

A minor vesicotomy was performed, with a urinary catheter introduced into the bladder. To decrease heat loss, a heating pad (Operatherm 200WTM, KanMed, Bromma, Sweden) was set to 38°C throughout the experiment. After the preparation was completed, we allowed a 30-min stabilization period before baseline values were registered and baseline blood samples were collected.

Protocol

The pigs were randomly allocated to 1 of 2 groups: endotoxemic group ($n = 19$) or control group ($n = 8$). Endotoxemic shock was induced in pigs by a 6-h-long continuous infusion of *Escherichia coli* endotoxin (*E. coli*: O111:B4; Sigma Chemicals, St. Louis, MO) in a dose of $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Arterial and sinus blood samples were collected at baseline and then hourly. At

the same time points, cardiac output was measured with the thermodilution method and physiologic data were registered (e.g., airway pressures from the respirator). The pigs were killed at the end of the experiment with an IV potassium chloride injection, after which brain biopsies were taken from the frontoparietal convexity of the left hemisphere.

Laboratory Assays

Arterial and mixed venous blood gas tensions and oxygen saturation, pH, base excess, and hemoglobin were analyzed (ABL™ 5 and Hemoximeter™, Radiometer, Brønshøj, Denmark). S100B was measured by CanAg S100 EIA assay (Fujirebio Diagnostics, Gothenburg, Sweden). The monoclonal antibodies in the enzyme-linked immunosorbent assay are raised against bovine S100B. CanAg S100 is a sandwich assay performed in microstrips coated with streptavidin; this S100 assay measures an equal amount of S100A1B and S100BB. The detection limit for S100 was <10 ng/L. The analytical precisions of S100 were 1.3%–2.5% coefficient of variation (intraassay) and 1.5%–2.5% coefficient of variation (interassay). An upper reference level of 90 ng/L was established for CanAg S100 by the manufacturer in healthy humans.

Immunohistochemistry

The streptavidin-biotin technique was used for immunohistochemistry. Unless otherwise stated, all incubations were performed at room temperature. Between each step, the sections were rinsed 3 times for 5 min with Tris-buffered saline, pH 7.4. The sections were deparaffinized in xylol and then rehydrated in a graded series of ethanol according to standard procedures. Antigen retrieval was performed by microwave treatment in a sodium citrate buffer (10 mM, pH 6.0; Zymed Laboratories, South San Francisco, CA) for 5 min. The slides were air dried and fixed in ice-cold acetone/methanol (1:1) for 15 min. Nonspecific binding was blocked with 5% normal horse serum in Tris-buffered saline (S-2000, Vector Laboratories, Burlingame, CA) for 1 h. Sections were incubated with primary anti-S100B antibody (Fujirebio Diagnostics) overnight at +4°C. After washing, the sections were incubated with a biotinylated horse anti-mouse secondary antibody (1:600, BA-2000, Vector Laboratories) for 60 min before incubation with horseradish peroxidase-streptavidin for 60 min. The antigen-antibody reaction was visualized using 3′3-diaminobenzidine as chromogen (S-300010, DAKO, Glostrup, Denmark). After washing, the sections were counterstained with Mayer's hematoxylin, dehydrated, and mounted (Pertex, Histolab products, Gothenburg, Sweden). Negative controls were performed by replacing the primary antibodies with nonimmune isotype-matched irrelevant monoclonal mouse immunoglobulin G (X 0931, DAKO) at the same concentrations as those of the corresponding primary antibodies.

Scoring Analysis of Immunoreactivity

Because immunohistochemistry is a more qualitative than quantitative method, the pattern of staining was characterized as being mainly focal or generalized and mainly vascular or glial in addition to the grading of staining intensities. An area was regarded as positive when the staining intensity was stronger than that found in the corresponding negative control. One person evaluated the immunohistochemical staining blindly as to which group the samples belonged. A score was assigned semiquantitatively on a 4-point scale from 0 to 3, where 0 indicated no staining, 1 less than one-third of the area stained, 2 more than one-third but less than two-thirds stained, and 3 more than two-thirds stained. The 2 compartments (blood vessels and glial cells) were scored separately.

Calculations

The following formulas were used: oxygen delivery (mL/min) = cardiac output × hemoglobin × arterial oxygen saturation × 1.34 mL O₂/g hemoglobin; static pulmonary compliance (mL/cm H₂O) = tidal volume/airway pause pressure.

Statistics

The distributions of all variables were tested for normality using the Kolmogorov-Smirnov test with $D > 0.10$ considered as nonnormal distribution. Arterial S100B concentrations and sinoarterial differences at specific time points were compared with *t*-test for independent samples. For comparison between groups over the whole study period, 1–6 h, repeated-measures analysis of variance was used. Differences in histological scores were assessed with the Mann-Whitney test. Data from nonsurviving animals were included from every completed hour of the experiment. A *P* value <0.05 was considered significant. Values are given as mean ± SE unless stated otherwise. The software STATISTICA 8.0 (StatSoft, Tulsa, OK) was used in the statistical calculations.

RESULTS

The animals were comparable in baseline characteristics. All endotoxemic pigs developed typical signs of endotoxemic shock with pulmonary hypertension, hypoperfusion, and organ dysfunction (Table 1). Three pigs in the endotoxemic group died (1 in the second hour and 2 in the fourth hour of the experiment).

S100B

At baseline, arterial, sinus, and sinoarterial concentrations did not differ between the groups (Table 2). In the endotoxemic animals, the arterial S100B concentration reached peak concentrations of 442 ± 33 and 421 ± 24 ng/L after 1 and 2 h, respectively, which were significantly higher than corresponding values in the nonendotoxemic animals of 306 ± 28 and 261 ±

Table 1. Physiologic Variables

| | Time (h) | Endotoxemic animals | Nonendotoxemic animals |
|--|----------|---------------------|------------------------|
| Mean arterial blood pressure (mm Hg) | 0 | 100 ± 14 | 93 ± 14 |
| | 1 | 90 ± 21 | 114 ± 24 |
| | 2 | 85 ± 21 | 106 ± 19 |
| | 3 | 86 ± 18 | 107 ± 16 |
| | 4 | 91 ± 21 | 111 ± 14 |
| | 5 | 96 ± 15 | 112 ± 13 |
| | 6 | 96 ± 18 | 114 ± 12 |
| Mean pulmonary arterial blood pressure (mm Hg) | 0 | 16 ± 1 | 16 ± 2 |
| | 1 | 30 ± 6 | 17 ± 2 |
| | 2 | 33 ± 5 | 18 ± 2 |
| | 3 | 36 ± 4 | 18 ± 2 |
| | 4 | 34 ± 6 | 19 ± 2 |
| | 5 | 33 ± 7 | 20 ± 2 |
| | 6 | 32 ± 6 | 20 ± 2 |
| Hemoglobin (g/L) | 0 | 87 ± 7 | 90 ± 8 |
| | 1 | 97 ± 8 | 86 ± 8 |
| | 2 | 101 ± 7 | 85 ± 8 |
| | 3 | 103 ± 8 | 82 ± 9 |
| | 4 | 103 ± 9 | 81 ± 8 |
| | 5 | 100 ± 10 | 79 ± 10 |
| | 6 | 96 ± 9 | 79 ± 11 |
| Oxygen delivery (mL/min) | 0 | 417 ± 78 | 423 ± 84 |
| | 1 | 493 ± 124 | 388 ± 46 |
| | 2 | 419 ± 113 | 365 ± 32 |
| | 3 | 345 ± 92 | 358 ± 50 |
| | 4 | 324 ± 90 | 374 ± 61 |
| | 5 | 349 ± 94 | 399 ± 112 |
| | 6 | 386 ± 103 | 391 ± 75 |
| pH | 0 | 7.46 ± 0.03 | 7.48 ± 0.03 |
| | 1 | 7.38 ± 0.05 | 7.47 ± 0.03 |
| | 2 | 7.37 ± 0.06 | 7.48 ± 0.03 |
| | 3 | 7.34 ± 0.07 | 7.48 ± 0.04 |
| | 4 | 7.34 ± 0.08 | 7.48 ± 0.04 |
| | 5 | 7.33 ± 0.07 | 7.46 ± 0.04 |
| | 6 | 7.34 ± 0.08 | 7.46 ± 0.03 |
| Base excess (mmol/L) | 0 | 4 ± 2 | 5 ± 2 |
| | 1 | 0 ± 2 | 4 ± 1 |
| | 2 | 0 ± 2 | 4 ± 2 |
| | 3 | -2 ± 3 | 3 ± 2 |
| | 4 | -3 ± 3 | 3 ± 2 |
| | 5 | -3 ± 3 | 2 ± 2 |
| | 6 | -3 ± 3 | 2 ± 2 |
| Static pulmonary compliance (mL/cm H ₂ O) | 0 | 8.8 ± 2.0 | 8.4 ± 1.1 |
| | 1 | 6.6 ± 2.1 | 7.7 ± 1.1 |
| | 2 | 5.4 ± 1.8 | 7.3 ± 1.2 |
| | 3 | 4.5 ± 1.8 | 7.2 ± 0.9 |
| | 4 | 4.4 ± 2.0 | 6.8 ± 1.1 |
| | 5 | 4.4 ± 2.2 | 6.4 ± 0.8 |
| | 6 | 4.3 ± 2.0 | 6.4 ± 0.8 |
| Diuresis (mL/h) | 1 | 85 ± 80 | 132 ± 73 |
| | 2 | 290 ± 180 | 142 ± 107 |
| | 3 | 112 ± 145 | 165 ± 100 |
| | 4 | 60 ± 55 | 215 ± 140 |
| | 5 | 52 ± 62 | 250 ± 200 |
| | 6 | 67 ± 81 | 240 ± 132 |

Data are presented as mean ± sd, except for diuresis, which is presented as median ± interquartile range.

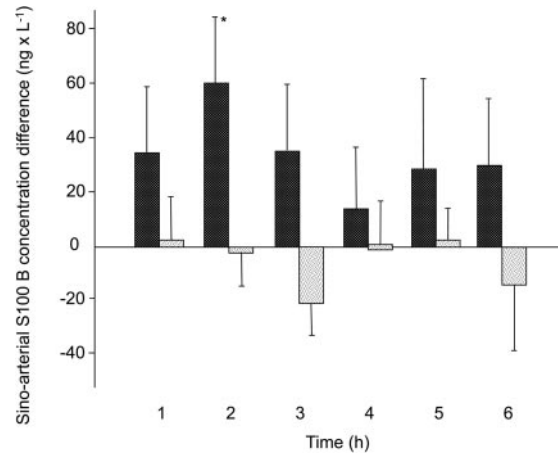


Figure 1. Brain sinoarterial S100B concentration differences over time after exposure to endotoxin infusion (dark bars) or saline (light bars). Data are presented as mean ± se. *Denotes significance, $P < 0.05$.

25 ng/L ($P = 0.018$ and 0.00053 , respectively). Thereafter, there was a gradual decrease to 290 ± 39 ng/L at 6 h with no significant differences to the control animals during the last 2 h. For 1–6 h, arterial S100B levels were higher in endotoxemic animals compared with controls ($P = 0.017$).

Sinoarterial concentration differences in S100B between superior sagittal sinus and arterial samples at different time points after exposure to endotoxin are demonstrated in Figure 1. In the endotoxemic animals, higher mean S100B concentrations were found in the superior sagittal sinus at all time points, whereas this was not seen in the control animals. As expected, the variations in the sinoarterial differences were large and statistically higher sinus versus arterial S100B concentration was only found at 2 h in the endotoxemic animals ($P = 0.033$). In the 3 nonsurviving endotoxemic animals, high sinoarterial concentration differences of 147 ± 33 and 147 ± 84 ng/L after 1 and 2 h, respectively, were recorded. When the sinoarterial concentration differences were compared between the groups for the whole study period, 1–6 h, values did not reach statistical significance.

Immunohistochemistry

The brains of the endotoxemic pigs demonstrated edema both macro- and microscopically. In the tissue

Table 2. Superior Sagittal Sinus and Arterial S100B Levels (ng/L) During the Experiment in Endotoxemic Pigs and Controls (Mean ± se)

| Time (h) | Endotoxemic animals | | Control animals | |
|----------|---------------------------|------------------------------|---------------------------|------------------------------|
| | Sinus S100B concentration | Arterial S100B concentration | Sinus S100B concentration | Arterial S100B concentration |
| 0 | 482 ± 38 ^a | 426 ± 26 | 428 ± 55 | 375 ± 29 |
| 1 | 478 ± 30 | 442 ± 33 | 309 ± 23 | 306 ± 28 |
| 2 | 481 ± 37 | 421 ± 24 | 258 ± 21 | 261 ± 25 |
| 3 | 411 ± 36 | 374 ± 22 | 199 ± 17 | 236 ± 26 |
| 4 | 352 ± 28 | 339 ± 26 | 200 ± 12 | 218 ± 25 |
| 5 | 331 ± 32 | 302 ± 36 | 203 ± 23 ^a | 196 ± 28 |
| 6 | 321 ± 37 | 290 ± 39 | 173 ± 15 | 203 ± 22 |

^a Missing data from 1 animal.

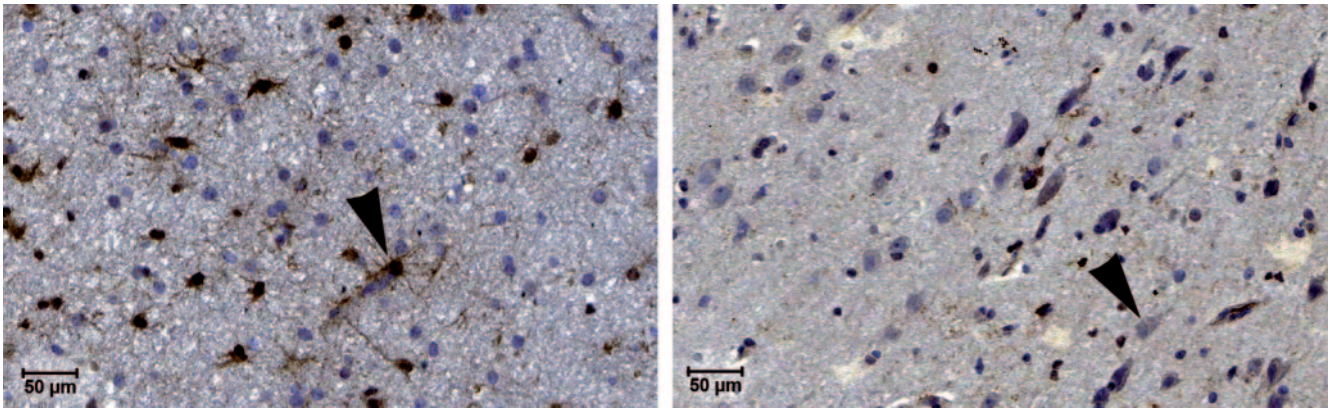


Figure 2. Left, Distribution of S100B in the brain of an endotoxemic animal. The main staining is seen in the astrocytes (arrow), both as nuclear and cytoplasmic staining. Furthermore, a weak staining is noted in the neuropil whereas the neurons are negative. Right, S100B immunostaining of the brain tissue in a nonendotoxemic animal. Only weak focal staining of glia cells are seen (arrow). The neural cells are negative.

sections, immunohistochemical localization of S100B demonstrated that the staining most often had a focal distribution, implying that areas with strong staining coexist with unstained or weakly stained areas within the same section. The staining was in general more intense closer to the surface area of the brain and weaker in the vicinity of vessels. In glial cells (mainly astrocytes), the protein was observed in the nucleus, cytoplasm, and extensions (Fig. 2). Moreover, the surrounding tissue (neuropil) was weakly positive. The focal glial S100B expression was more intense in the endotoxemic pigs (median score: 1; interquartile range: 0.8–2) than in the nonendotoxemic controls (median score: 0; interquartile range: 0–0.3) ($P = 0.0047$), whereas general glial S100B expression was equally intense in these groups. No difference was noted in S100B expression in the brain endothelium in endotoxemic versus nonendotoxemic pigs.

DISCUSSION

This study showed that cerebral postcapillary blood taken from the superior sagittal sinus contained higher S100B concentrations than systemic blood from an artery in the endotoxemic group at the time point of highest S100B release. The endotoxemic pigs had a higher concentration of S100B than nonendotoxemic animals in both central arterial and sinus blood. Furthermore, in the endotoxemic animals, S100B was expressed to a higher grade in the brain, mainly in the astrocytes. We therefore conclude that the central nervous system is an important source for this protein in plasma during endotoxemia.

If S100B was constantly liberated into the circulation from the brain as a sole source, its concentration in superior sagittal sinus blood would be higher than system blood levels at all times, although factors such as rate of S100B liberation, cerebral blood flow, and the half-life of S100B would affect the magnitude of the concentration difference. In this study, the mean S100B concentrations were higher than the S100B concentrations in the superior sagittal sinus; however,

there was a wide range in concentration differences, and in some of the matched samples, S100B levels were higher in arterial blood than in blood from the superior sagittal sinus, both in endotoxemic and nonendotoxemic pigs. Several explanations of this variation may be possible in endotoxemia: other organs than the brain may release S100B, the release of this protein from the brain may be intermittent, or S100B could reach the sinus circulation via the cerebrospinal fluid (CSF) leading to a delayed uptake of this protein. The organs from which S100B is released may differ among animals. The reason for this may be that the individual response to endotoxin may vary in the pattern and severity of organ dysfunction, even though a standardized dose of endotoxin was given to this relatively homogenous population of laboratory animals. Another possible explanation for the variation in sinoarterial concentration differences could be an intermittent release of S100B from the brain. However, this event is less likely to occur because the half-life of S100B in human circulation is in the magnitude of 30 min,³¹ which is considerably longer than the time required for sinoarterial equilibration. S100B uptake in the sinus circulation indirectly from the CSF would be another option, but this would probably occur with a delay of several hours. This alternative needs further investigation including analysis of the CSF concentration over time. However, all these effects would only be able to yield higher arterial versus sinus S100B concentrations if S100B uptake would take place in the brain, which has not been described and is therefore most unlikely.

In this study, S100B levels were higher at baseline than at the end of the experiment in both groups (Table 2). The higher baseline values of S100B may have been due to trauma of S100B-containing tissues such as fat when inserting catheters for cardiovascular monitoring or due to release from the central nervous system when the structures close to the brain were manipulated during the insertion of a catheter into the superior sagittal sinus despite the meticulous surgical

technique. However, this has not affected the result, because there were no statistical differences in these baseline values between the groups and, in contrast to the endotoxemic group, S100B levels in the control group decreased rapidly.

Immunohistochemistry in this study showed a non-uniform distribution of S100B expression (mainly in glial cells) in the brain tissue. The expression of S100B in glial cells in focal areas of the brain tissue was more frequent and more intense in endotoxemic animals than in nonendotoxemic controls, whereas the abundance or intensity of the general or vascular expression did not differ between the 2 groups. Therefore, S100B is expressed increasingly in areas relatively distant from cerebral vessels in endotoxemia, whereas areas adjacent to the vessels are not affected. These findings may indicate that glial cells in areas with larger distance to nutritional supply and higher vulnerability to ischemia are more prone to express S100B. Alternatively, the vicinity of vessels could facilitate the washout of S100B into the circulation. The discharge of S100B from the brain is described in BBB damage.^{14,15} In this sepsis model, increased permeability of the BBB could be present because increased capillary permeability is observed in many other vascular beds, as suggested by peripheral edema formation, hemoconcentration, and decreasing pulmonary compliance. Furthermore, charged proteins (such as S100B) have very poor ability to penetrate the tight junctions of the BBB, and increased plasma levels of S100 may not necessarily follow increased glial production of this protein unless BBB damage is present.³²

Assessment of encephalopathy was not possible in this experiment because the animals were anesthetized during the experiment. It cannot be excluded that S100B may have been released as a direct effect of endotoxin without cerebral pathology. However, several organs (e.g., the lungs and kidneys) demonstrated dysfunction in this septic model. This, as well as the presence of cerebral edema, indicate that cerebral dysfunction was probably present in these animals. Moreover, a decreased level of consciousness has been described in experimental animals in response to endotoxin.³³

The role of S100B has been studied in both experimental and clinical settings. In 1 experimental study, increased plasma levels of S100B were described in endotoxemia, and it was postulated that disruption of the BBB could be the reason for this event.²⁶ The experimental set-up used in that study, as pointed out by the authors and others,³⁴ did not make conclusions on the organ origin of S100B in a sepsis model possible. Moreover, 2 clinical studies indicated conflicting results on the issue of S100B levels and brain dysfunction in sepsis. In 1 of these clinical studies, Nguyen et al.²⁴ found that encephalopathy in sepsis was more frequently observed in patients with increased S100B serum levels. However, in the other

study, Piazza et al.²⁵ found no correlation between S100B levels and encephalopathy scales or neurological outcome. The bulk of knowledge on S100B in sepsis and endotoxemia is therefore increasing, but a better understanding of this brain damage marker is required if it is to be included in the routine diagnostic arsenal in septic encephalopathy.

Our results support the hypothesis that the brain is a source of S100B in endotoxemia even though there may be other sources. These findings make S100B a candidate as a marker of cerebral dysfunction in septic shock.

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The Long-Term Effect of Four Hours of Hyperventilation on Neurocognitive Performance and Lesion Size After Controlled Cortical Impact in Rats

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BACKGROUND: We investigated the effects of 4 h of posttraumatic hyperventilation on neurocognitive performance, motor function, and coordination as well as lesion volume in rats subjected to focal traumatic brain injury.

METHODS: After a 14-day training period with various neurocognitive tests including hole-board, beam walk, and beam balance, 21 male Sprague-Dawley rats (369 ± 15 g) were anesthetized with halothane, tracheally intubated, their lungs mechanically ventilated, and subjected to controlled cortical impact (1.75 mm depth, \emptyset 5 mm, 4 m/s). They were then randomized to either normoventilation ($n = 10$; $\text{Paco}_2 = 38\text{--}42$ mm Hg) or hyperventilation ($n = 11$; $\text{Paco}_2 = 28\text{--}32$ mm Hg) and ventilated for 4 h, respectively. Posttraumatic performance in the behavioral and motor tests was evaluated for 20 days. Rats were then decapitated under deep anesthesia, and their brains frozen and sliced to evaluate lesion volume.

RESULTS: Hyperventilated animals performed significantly worse in explicit memory tests compared with normoventilated rats over time. Both groups showed deficits in advanced motor function and coordination (evaluated by beam walk and beam balance) initially, with a significantly worse performance of hyperventilated compared with normoventilated animals. However, there was no difference between groups by the end of the study. On Day 20 after injury, lesion volume was significantly larger with hyperventilated (69.7 ± 13.0 mm³) compared with normoventilated animals (48.3 ± 15.6 mm³).

CONCLUSIONS: Although hyperventilation enhanced histologic damage, there was no long-term adverse neurocognitive effect from 4 h of posttraumatic hyperventilation ($\text{Paco}_2 = 28\text{--}32$ mm Hg) in rats.

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Minimizing secondary injury after brain trauma is the primary goal of cerebral resuscitation. Induced hypocapnia can lead to a lifesaving reduction of

intracranial pressure through cerebral vasoconstriction in patients with severe intracranial hypertension after cerebral trauma. Hyperventilation to Paco_2 of approximately 25 mm Hg has been one of the cornerstones in the management of traumatic brain injury for >45 yr. Evidence suggests that hyperventilation of 5 days' duration in critically ill patients may adversely affect outcome.¹ Moreover, it has been demonstrated in acute studies using various biochemical and metabolic indices that hyperventilation might turn borderline ischemia that is present after severe head trauma into frank ischemia, which will lead to neuronal cell death.^{2,3} Despite the absence of any outcome studies with hyperventilation for <5 days, the Brain Trauma Foundation guidelines recommend that chronic prolonged hyperventilation therapy should be avoided after severe traumatic brain injury but that hyperventilation for brief periods may be necessary in the management of neurologic deterioration. Neither "prolonged" nor "brief periods" are defined.⁴ To address the absence of outcome data on the effect of short periods of hyperventilation, we investigated the effects of 4 h posttraumatic mild to moderate hyperventilation on neurocognitive and advanced motor function and coordination as well as lesion volume in

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rats up to 3 wk after focal traumatic brain injury. We hypothesized that this period of hyperventilation would have no demonstrable effect compared with normocapnia.

METHODS

The study was approved by the institutional animal care committee and performed in accordance with the German animal protection law "Deutsches Tierschutzgesetz." Twenty-one male Sprague-Dawley rats (50 g) were delivered from Charles River Laboratories (Kisslegg, Germany) 42 days before operation day and kept in the animal facilities under standard laboratory conditions (12 h light/12 h dark, lights on at 6:00 AM, 22°C, 60% humidity, and free access to water and standard rat chow). Rats were acclimatized in groups for 3 wk. Another week was allowed for habituation to the home cage and attached test arena before starting the 2-wk training period.

Hole-Board Test

The cognitive performance was evaluated by investigators blinded to treatment allocation using the modified hole-board test.^{5,6} This test was designed to investigate cognitive, exploratory, and motivational variables in rats without negative enforcement. The home cage and the test arena were separated from each other by a transparent partition, perforated with holes to allow visual and olfactory contact between group mates. The hole board (20 × 40 cm) was placed in the middle of the test arena. The board was made of opaque gray polyvinyl chloride with 15 holes staggered in 3 lines covered by lids, which could easily be opened. After opening, coil springs forced the lids immediately back to their original position. Three lids were marked with white adhesive tape (every day different lids) and contained a food reward (puffed rice). All holes were flavored with the aroma of black currants (black currant flavor dissolved in water; concentration 0.02%) to cover the odor and smell of the puffed rice.

Seven days before the cognitive training period, all animals were habituated to the testing environment. During this phase, the partition was removed and the animals were allowed to explore both the test arena and the home cage compartment. During habituation, the holes of the board were neither marked nor baited. After being returned to their home cage, the animals received several pieces of puffed rice to habituate to the food reward.

During the training phase, rats were tested for 4 trials a day for 14 successive days with marked and baited holes. The sequence of marked holes was randomly changed every day. With completion of the training period, baseline conditions were obtained for 3 days. The following day, animals underwent surgical preparation with induction of controlled cortical impact (see below). After surgery, the animals were

returned to their home cages for daily testing for 20 days.

The main variable evaluated with the hole-board test was deficits within the declarative or explicit memory. Deficits were assumed if rats visited non-baited holes or did not visit baited holes referred to as wrong choices. Other observations included anxiety-related behavior (prolonged latency to enter the open field of the board) and exploratory motivation, which was assumed if the rats hesitated to search for the rewards (latency hole visit) or were not interested in their environment (i.e., showed less grooming behavior).

Neurologic Tests

To evaluate advanced motor function and coordination, a beam walk (number of wrong steps with the left hindpaw) and beam balance test (maximum 60 s) were performed. The beam for the walk test was 2.5 cm, and the beam for the balance test was 1.5 cm wide. Both were 130 cm long and placed 60 cm above the ground. During the 3 days before controlled cortical impact, rats were trained, and after controlled cortical impact, rats were tested for 20 days.

Additionally, awareness, grooming, ability to walk and climb, force on a rotating screen, and prehensile traction were assessed daily as described previously⁷ and summarized as activities of daily living.

Preparation

On the day of trauma induction, fasted rats (369 ± 15 g) were anesthetized in a bell jar saturated with halothane. Rats were then tracheally intubated and their lungs mechanically ventilated (Harvard Rodent Ventilator, Model 683, Harvard Apparatus, South Natick, MA, Paco₂ = 38–42 mm Hg, Capnomac, Datex, Helsinki, Finland) with 1–1.5 vol% halothane in N₂O/O₂ (FIO₂ = 0.33). Catheters were inserted in the tail artery for continuous arterial blood pressure measurement and blood sampling and in the femoral vein for administration of norepinephrine if needed. Temperature probes were placed in the right temporal muscle and the rectum. Pericranial temperature was maintained constant during the experiment at 37.5°C using a servo-controlled overhead heating lamp. Also, needle electrodes were inserted subcutaneously to record electrocardiogram and measure heart rate (Cadiocap II, Datex). Rats were then placed in a stereotactic "U"-frame (Model 962, Kopf Instruments, Tujunga, CA) using atraumatic ear bars. After a midline incision, the scalp was retracted, exposing the right parietal bone. A 6-mm craniotomy was performed between bregma and lambda, and the coronal ridge using a high-speed dental drill with a 0.9-mm tip cooled with lactated Ringer's solution. After drilling 3 sides without injuring the dura mater, the bone flap was opened over the sagittal suture.

The controlled cortical injury device (SHT-3 CCI Controller, custom made, Johannes Gutenberg-Universität, Mainz, Germany)^{8,9} consisted of a pneumatic cylinder rigidly mounted on a crossbar. On the lower end of

the rod, the impact tip (5 mm in diameter) was attached (i.e., the shaft that comes into contact with the exposed dura). To induce controlled cortical impact, this tip was vertically driven at a predetermined velocity (4 m/s), depth (1.75 mm), and duration (200 ms) of brain deformation.

Ten minutes before adjustment of the impact tip, shaft halothane concentration was decreased to 0.8 vol%, and baseline measurements were taken. After controlled cortical impact induction, animals were immediately removed from the injury device, the bone flap was closed and sealed with histoacrylic glue (Histoacryl, B. Braun, Tuttlingen, Germany). The scalp incision was closed with interrupted sutures, and 0.2 mL of bupivacaine 0.5% (Curasan AG, Kleinostheim, Germany) was infiltrated. Nitrous oxide was now replaced by air ($F_{IO_2} = 0.33$), and animals were then randomized to either normoventilation ($n = 10$; $Paco_2 = 38\text{--}42$ mm Hg) or hyperventilation ($n = 11$; $Paco_2 = 28\text{--}32$ mm Hg) and their lungs ventilated for 4 h, respectively. During this period in both groups, physiologic variables were continuously monitored, maintained stable, and documented shortly after controlled cortical impact (0.00), after 1:00, 2:30, and 4:00 h (respiratory rate, pH, and glucose). Mean arterial blood pressure was kept constant by intermittent low-dose IV injection of norepinephrine (Arterenol, Aventis Pharma, Frankfurt a. M., Germany, $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). After 4 h of posttraumatic ventilation, catheters were removed and the incisions closed and infiltrated with 0.2 mL bupivacaine 0.5%. After weaning from ventilation and tracheal extubation, the completely awake rats received buprenorphine 0.03 mg subcutaneously as analgesia and were returned into the hole-board cage.

On Day 20, animals were killed by decapitation in deep anesthesia and brains were removed and frozen at -70°C . From each animal, sets of 11 consecutive coronal $10\text{-}\mu\text{m}$ cryostat brain sections with 1-mm intervals from a defined zero point (macroscopically visible morphologic formation at $-1600 \mu\text{m}$ ante bregma, Plate 11) were cut and mounted.¹⁰ These sections were stained with cresyl violet and examined by 1 investigator blinded to the treatment conditions.

The cresyl violet-stained coronal sections were digitized using a camera (Evolution MP Camera, Media Cybernetics, Silver Spring, MD). The lesion area was measured by determining the cross-sectional injury in each image and multiplied by the exact thickness of the tissue between the slices. This slab volume technique was implemented on the image processing program Image-Pro Express 4.5 and created the lesion volume (in mm^3) (Media Cybernetics).

Statistical Analysis

Hemodynamic, biochemical, and blood gas variables were subjected to a 2-way analysis of variance with the within-groups factors time^2 , the between-group factor ventilation, and their interaction term

($\text{time}^2 \times \text{ventilation}$). If this interaction term was significant ($P < 0.05$), *post hoc* analyses were performed in a hierarchical manner by Bonferroni-corrected *t*-tests or paired *t*-tests. Effects of time levels were analyzed quadratically (time^2) for physiologic as well as neurologic and cognitive values, focusing on biphasic changes of these variables during the observation period.

The variables of the modified hole-board test and those of the neurologic tests were subjected to a 2-way repeated-measurement analysis of variance with the within-group factor, postoperative day, the between-groups factor ventilation, and all possible interaction terms. *Post hoc* analyses were performed in a hierarchical manner by Bonferroni-corrected *t*-tests.

Lesion volume and lesion area were analyzed using *t*-test with the 2 groups as independent variables. The sample size estimate was based on a critical difference of $2 \times \text{SD}$ of at least 1 quality of brain function, i.e., cognitive, motor, behavioral, or sensory function. A power of 0.9 and an $\alpha < 0.05$ was defined. Alpha was divided by 4 to address the 4 possible reasons for a difference (repeated measurements). The number calculated by this technique was $n = 8$ but we increased to $n = 10$ to address the complexity of the project.

Continuous data were expressed as mean \pm SD and presented in figures as mean \pm SEM. $P > 0.05$ was considered significant. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Chicago, IL).

RESULTS

One animal of the hyperventilated group died on Day 1 after controlled cortical impact for unknown reasons. The frozen brain from 1 animal of the normoventilated group was damaged and therefore lost for histologic evaluation. Results of the behavioral tests of the normoventilated animal and physiologic variables of both animals were included in the analysis.

Differences in physiologic data before and after controlled cortical impact are shown in Table 1. There was a study-related marked increase in respiratory rate and pH in the hyperventilated group compared with the normoventilated group and baseline levels. Blood glucose levels decreased over time with values always within the physiologic range of rats. There were no differences in mean arterial blood pressure (90 ± 10 mm Hg), heart rate (325 ± 25 bpm), or pericranial temperature (37.5°C) and at no time were rats hypoxemic (Pao_2 : 125 ± 15 mm Hg).

Animals in the hyperventilated group showed a significant deficit in declarative (explicit) memory on Days 1 and 2 after controlled cortical impact compared with baseline and over time compared with the normoventilated group ($\text{time}^2 \times \text{group}$, $P < 0.05$) (Fig. 1). There were no differences in any anxiety-related or motivational variables between groups (Fig. 2). Both groups showed motor function and coordination deficits in the beam walk and beam balance test for the

Table 1. Physiologic Variables

| | | Time | | | | |
|-----------------|------------------|-------------|---------------|---------------|---------------|---------------|
| Group | | Baseline | 0.00 | 1.00 | 2.30 | 4.00 |
| RR (per min) | Normoventilation | 49 ± 4 | 47 ± 4 | 46 ± 5 | 47 ± 5 | 48 ± 4 |
| | Hyperventilation | 50 ± 5 | 83 ± 8*† | 77 ± 11*† | 81 ± 14*† | 80 ± 13*† |
| pH | Normoventilation | 7.42 ± 0.02 | 7.44 ± 0.01 | 7.41 ± 0.02 | 7.41 ± 0.02 | 7.41 ± 0.02 |
| | Hyperventilation | 7.41 ± 0.03 | 7.53 ± 0.04*† | 7.49 ± 0.02*† | 7.49 ± 0.03*† | 7.49 ± 0.03*† |
| Glucose (mg/dL) | Normoventilation | 130 ± 18 | 115 ± 14† | 108 ± 23† | 109 ± 23† | 107 ± 16† |
| | Hyperventilation | 142 ± 33 | 123 ± 29† | 121 ± 19† | 114 ± 12† | 117 ± 11† |

Respiratory rate (RR), pH, and plasma glucose concentration before controlled cortical impact (baseline), shortly (0:00), 1 h, 2.5 h, and 4.00 h after controlled cortical impact (mean ± sd).

* $P < 0.05$ normoventilation vs. hyperventilation at each time point.

† $P < 0.05$ vs. baseline.

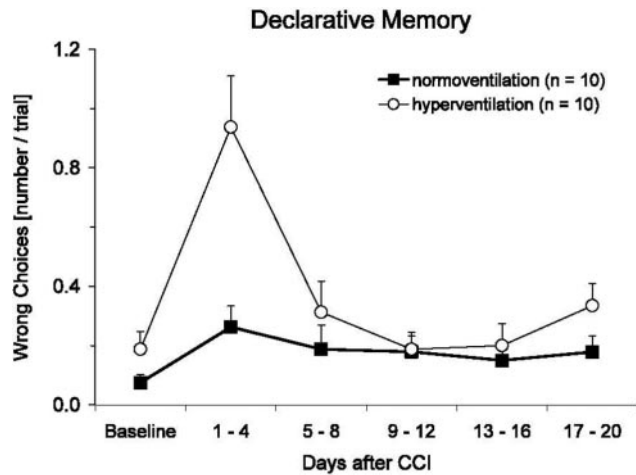


Figure 1. Hyperventilated animals had a significant deficit in declarative (explicit) memory on Days 1–4 after controlled cortical impact compared with baseline and over time compared with the animals in the normoventilated group (time² × group, $P < 0.05$).

first days after controlled cortical impact compared with baseline (Fig. 3). Overall, hyperventilated animals performed significantly worse than animals in the normoventilated group (time² × group, $P < 0.05$). In both groups, performance returned to baseline levels on Day 6. No differences between groups or comparisons with baseline were observed in awareness, grooming, ability to walk, climb, or apply force on a rotating screen, prehensile traction, anxiety-related behavior, and arousal.

Lesion volume (mm³) was significantly increased in hyperventilated animals (69.66 ± 13.01) compared with normoventilated animals (48.34 ± 15.6). Lesion areas (mm²) are shown in Figure 4.

DISCUSSION

The results of this study indicate that 4 h of hyperventilation (Paco₂ = 28–32 mm Hg) after controlled cortical impact transiently impairs declarative (explicit) memory and advanced motor function and coordination to a greater degree than normoventilation. Longer-term lesion volume after traumatic brain injury was significantly larger in hyperventilated animals. Activities of daily living were not affected by traumatic brain injury or mode of ventilation in rats.

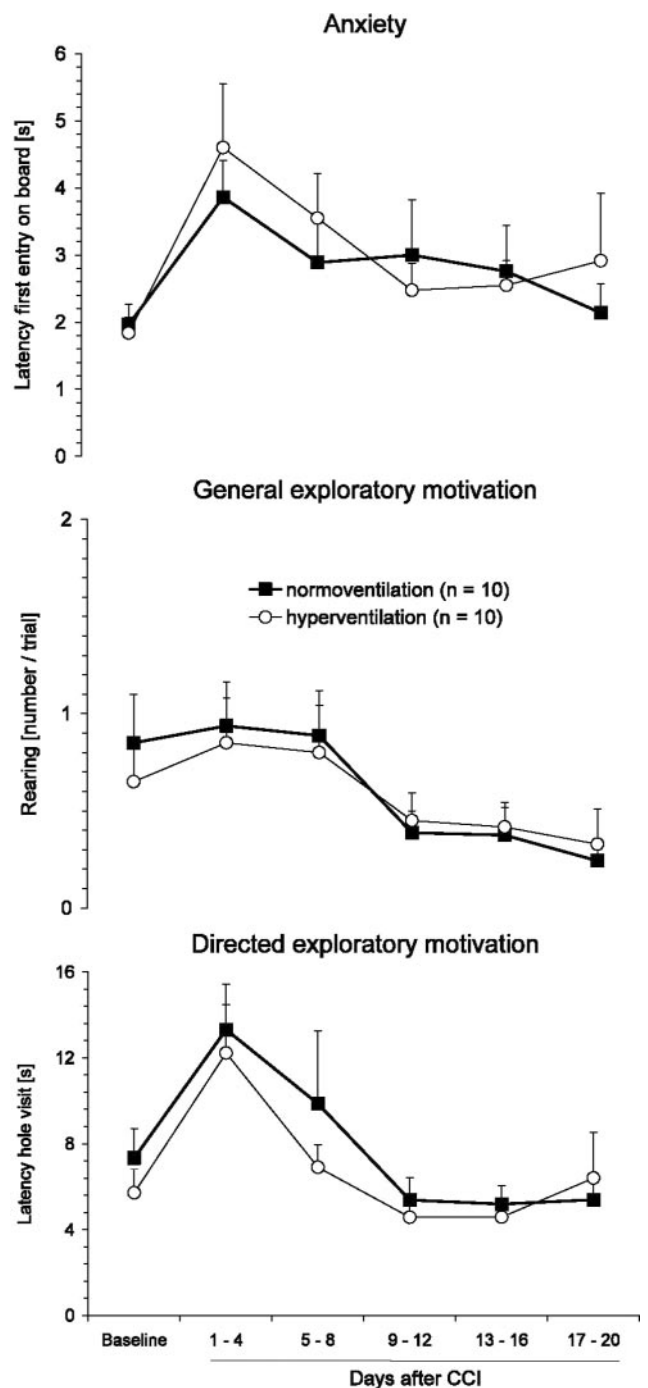


Figure 2. Anxiety and exploratory motivation. There were no differences between groups for these measures.

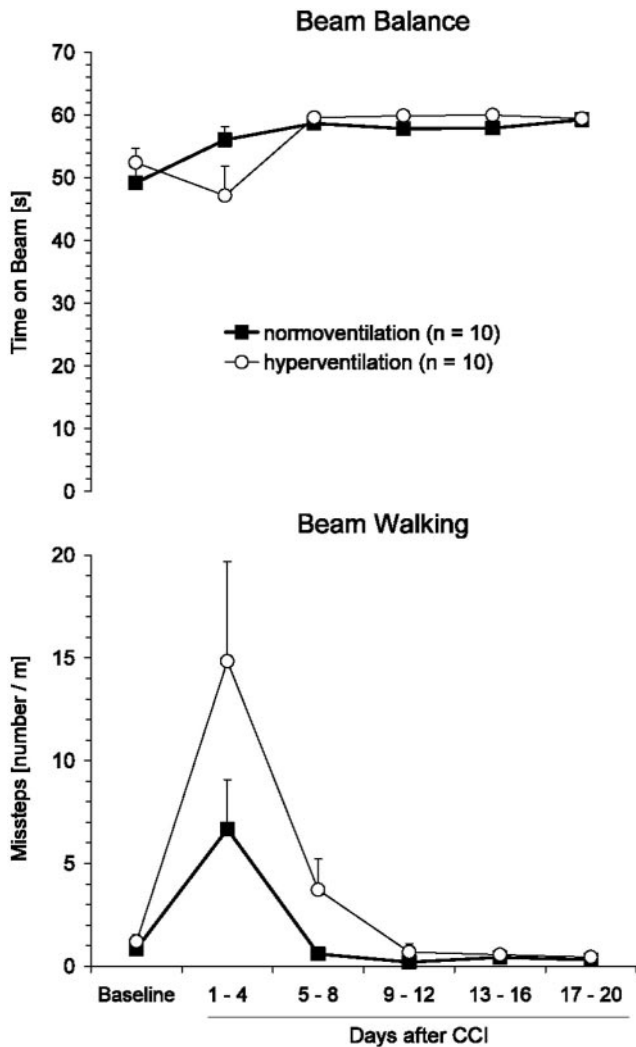


Figure 3. Motor function and coordination. Both groups showed motor function and coordination deficits in the beam walk after controlled cortical impact compared with baseline. Hyperventilated animals performed significantly worse than normoventilated animals ($\text{time}^2 \times \text{group}$, $P < 0.05$). In both groups, performance returned to baseline levels on Day 6.

Severe traumatic brain injury is a major cause of morbidity and mortality, particularly among young men.¹¹ Experimental and clinical studies have shown that brain damage does not cease with the primary injury but progresses over subsequent hours and days. Subsequent or secondary injury occurs when factors not initially present worsen outcome, and cerebral ischemia is a common contributor. Treatment of the primary injury is virtually impossible; therefore, therapeutic management of patients with traumatic brain injury focuses on minimizing the extent of the secondary injury.

The use of hyperventilation, defined as the induction and maintenance of levels of Paco_2 less than the normal range (<35 mm Hg), in patients with head trauma has been advocated for >45 yr.¹² Its main effect is a decrease in intracranial pressure by cerebral arterial vasoconstriction with resultant decreased cerebral flow and blood volume. There is concern and

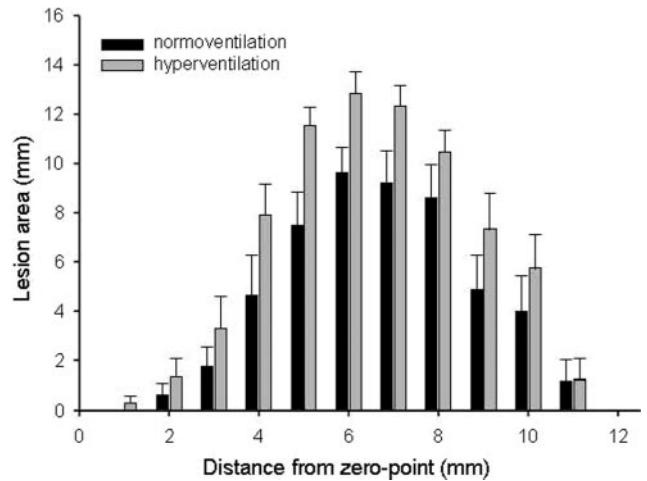


Figure 4. Lesion area after controlled cortical impact. Lesion volume (mm^3) was significantly increased in hyperventilated animals compared with normoventilated animals.

controversy whether the cerebral vasoconstriction may be excessive and lead to ischemia with worsening of secondary injury. The controversies have been extensively reviewed elsewhere.¹³ Briefly, biochemical surrogate end points such as glutamate and lactate have been shown to increase significantly.¹⁴ Many other surrogates have been used including jugular venous oxygen saturation¹⁵ and regional cerebral blood flow¹⁶ with many, but not all, studies showing a few minutes of hyperventilation worsening the measured variable. This type of study has prompted the Brain Trauma Foundation guidelines.

However, even with expert guidelines recommending against it,⁴ deliberate hyperventilation continues to be widely practiced. According to a survey conducted before the Brain Trauma Foundation guidelines were published, 83% of board-certified neurosurgeons in North America used prophylactic hyperventilation.¹⁷ Even though this proportion has significantly decreased after publication of the first Brain Trauma Foundation guidelines in 1995, 36% of neurosurgeons in North America still prophylactically hyperventilate patients with traumatic brain injury.¹⁷ Two years after this publication, a survey by Huizenga et al.¹⁸ showed that 47% of emergency clinicians would elect to use prophylactic hyperventilation despite guidelines recommending otherwise. In the same year, Thomas et al.¹⁹ were able to demonstrate that 60% of already intubated traumatic brain injury patients were hyperventilated, and 70% had an inappropriately high assisted ventilation rate during transport to the hospital. A more recent study found that only 30% of severe head trauma patients were transported with a Paco_2 in the appropriate target range.²⁰

Despite current recommendations, there is little clinical evidence for a worse outcome after relatively short periods of mild to moderate hyperventilation. The most recent Brain Trauma Foundation guidelines address this matter as a key issue for future investigations.⁴ Although our clinical interest was to crudely "mimic" transportation from the accident scene to the

hospital and initial evaluation and treatment or from the intensive care unit to imaging and then the operating room, we also needed to use a duration of hyperventilation long enough to actually produce a quantifiable injury. A previous study that used less sensitive behavioral testing and 5 h of hyperventilation found no difference in behavior but a worse histologic lesion.²¹ We estimated that using our more sensitive tests for 4 h would result in quantifiable injury that would allow detection of differences between groups if there were any.

To be able to broadly evaluate clinical outcome, several determinants including neurocognition (declarative memory, anxiety-related behavior, and arousal), advanced motor function and coordination (beam walk and beam balance test), activities of daily living, and anatomical variables (brain lesion volume) were studied. Declarative memory is the aspect of memory that stores facts and is a term for information that is available to conscious recollection and in people to verbal retrieval (i.e., it can be "declared"). Neurophysiologically, declarative memory requires the medial temporal lobe, especially the hippocampus and related areas of the cerebral cortex of the brain.²² Therefore, the extent and severity of a lesion in this area induced by the controlled cortical impact with secondary injury will impair the function of this memory system and is detectable by the hole-board test. The hole-board test has advantages over other cognitive tests used in animals, e.g., the Morris-water maze or the radial-arm maze.^{23,24} The rats are habituated with a minimum of stress. No food deprivation is necessary because the rats perform the test voluntarily, and little effort is needed for the rats to move the lid and find the reward.⁵ These factors likely enhance the motivation of the animals to perform the test in comparison with other cognitive tests. Furthermore, our use of a relatively long prehead trauma acclimation and training period makes continuing learning after the injury highly unlikely. A parallel experiment included a sham group, i.e., anesthesia but no brain injury, and the sham inhaled anesthetic group displayed no cognitive changes over time other than a brief period of motor (grooming) hyperactivity.²⁵

Using the modified hole-board test, animals that received controlled cortical impact treated with hyperventilation showed significant short-term (4 days) worsening of declarative memory compared with normocapnic animals. Because anxiety-related behavior, motivation, and activities of daily living were neither influenced by ventilatory treatment nor differed compared with baseline, our results suggest a hyperventilation-associated secondary functional lesion, i.e., cognitive dysfunction after controlled cortical impact.

Advanced motor function and coordination were impaired in both groups during the first days after traumatic brain injury with hyperventilated animals performing about 3 times worse than normoventilated

animals. A similar study in rats subjected to more aggressive hyperventilation ($Paco_2 = 20.3 \pm 0.7$ mm Hg) did not show differences between groups in a beam balance test.²¹ The trauma depth in that study was larger (2.5 mm compared with 1.75 mm), and rats were trained for only 1 day compared with 3 days in this study. These differences between studies might account for the different results.

The lesion volume in this study was significantly larger in the hyperventilated group, which is consistent with a worsening of the secondary injury. We evaluated lesion volume when scar formation was most likely completed, and there was minimal edema. Additional time points to assess histopathologic damage, for example, when secondary damage is most prominent (24 h to 3 days), would have been helpful to determine a time course of events. However, emphasis in this study was placed on longer-term outcome with sequential behavioral and motor function tests rather than tracking sequential histologic events. The traumatic brain injury model used is well characterized and creates a highly reproducible lesion in a very controlled fashion. Relevant stages of the pathophysiology of human traumatic brain injury, including contusion and axonal injury, are reproduced in this model. The evaluation, procedure, and compromising factors of this method were described elsewhere.²⁶

Animals in this study were fasted for 8 h with free access to water even though in hindsight there are suggestions that, when rats are handled stress-free and glucose levels range within normal limits, this would not have been necessary. Even hyperglycemic rats subjected to mild cortical impact injury had adverse effects only when a secondary ischemic insult was added after the impact injury.²⁷ Therefore, fasting versus nonfasting does not seem to be an important factor in controlled cortical injury models.

In conclusion, 4 h of posttraumatic mild to moderate hyperventilation ($Paco_2 = 28\text{--}32$ mm Hg) enhanced histologic damage but only transiently impaired neurocognitive performance, motor function, and coordination in rats subjected to traumatic brain injury. These experimental data, if clinically applicable, suggest that short-term hyperventilation as deliberately and inadvertently seen in traumatic brain injury patients immediately after the injury may cause transient neurocognitive deterioration but no long-term effect.

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References to Anesthesia, Pain, and Analgesia in the Hippocratic Collection

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The Hippocratic Collection, containing 60 medical texts by Hippocrates and his pupils, was searched using the electronic database Thesaurus Lingua Graeca to identify the words “anaesthesia” and “analgesia,” their derivatives and also words related to pain. Our purpose was to investigate the special use and meaning of these words and their significance in medical terms. The word “anaesthesia” appears 12 times in five Hippocratic texts to describe loss of sensation by a disease process. This observation reveals Hippocrates as the first Greek writer to use the word in a medical rather than a philosophical context. Hippocrates was also the first Greek physician to keep an airway open by bypassing a pharyngeal obstruction with the insertion of narrow tubes into the swollen throat of a patient with quinsy, thus facilitating the airflow into the lungs. In the Hippocratic texts, “analgesia” is related to “anaesthesia” for the first time, when it is pointed out that an unconscious patient is insensitive to pain. Hippocrates and his followers rationalized pain as a clinical variable and as a valuable diagnostic and prognostic tool. They used expressive and precise adjectives and well-defined characteristics of pain, such as location, duration, or relation to other symptoms, to elucidate a disease process. They also had a wide terminology for the various types of pain, still in use today. Many cures were described for the treatment of pain, including incisions, effusions, venesection, purges, cauterization and, most interestingly, the use of many plants, such as opium or the application of soporific substances. In particular, Hippocrates refers to opium poppy as “sleep inducing.”

(Anesth Analg 2010;110:188–94)

It is widely believed that the Greek philosopher Dioskourides was the first to use the word “anaesthesia”^{*} in the 1st century CE to describe the narcotic effects of the plant mandragoras (mandrake).¹ However, the word had been used by Greek scholars as a philosophical concept almost 5 centuries before it was used to describe a pharmacologic action.^{1,2} The historian Thucydides (460–400 BCE) described the word “anaesthesia” as “bluntness of perception”[†] to denote political indifference and disinterest,³ whereas in *Philebus* by Plato (427–348 BCE), the word has the philosophical meaning of “the oblivion of the soul from

the movements of the body” or “want of perception.”^{2,4} It is in the writings of Hippocrates (c. 460–380 BCE) that we find the word “anaesthesia” used for the first time in a medical context as loss of sensation and unconsciousness. The Hippocratic Collection, containing 60 articles, represented a canon for those studying medicine. Although not all were written by Hippocrates himself, and they are believed to be part of a library based at the School of Kos, they reflect medical concepts and practices for at least 4 centuries BCE, some of them still accepted by contemporary medicine.

The purpose of this study was to investigate the special use and meaning of ancient Greek words related to anesthesia, pain, and analgesia in the Hippocratic Collection and to relate some of them to modern Greek terms. It is the study of texts in their original language that helps us to improve our understanding of medicine and anesthesia in the 21st century.

METHODS

The words related to anesthesia, analgesia, and pain and their derivatives were searched in all 60 Hippocratic articles using the Thesaurus Lingua Graeca electronic program.⁵ This program is an electronic database of the entire ancient Greek literature,

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*Ancient Greek words using Latin characters are given in regular characters and inverted commas “. . .”

†English translations of original Greek texts are given in italic characters and inverted commas “. . .”

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Table 1. The Word “Anaesthesia” and Its Derivatives, Their Explanation in English and the Citations in the Hippocratic Collection Where These Words Appear^a

| Derivatives of the word “anaesthesia” | Explanation in English | Citation |
|---------------------------------------|--|--|
| “Anaesthesia” [αναίσθησις] (2) | Noun, meaning: loss of sensation, unconsciousness | <i>Coan Precognitions</i> , 466.1 <i>Letters</i> , 10th Letter, line 43 |
| “Anaesthetos” [αναίσθητος] (5) | Adjective, meaning: senseless | <i>Breaths</i> , 13.3 & 14.44 <i>Epidemics</i> , 7.1.1.21 <i>Coan Precognitions</i> , 395.3 <i>Use of Liquids</i> , 1.27–33 |
| “Anaesthetos” [αναίσθητως] (3) | Adverb, derived from the adjective “anaesthetos” [αναίσθητος] | <i>Epidemics</i> , 3.3.17.12 & 3.3.17.15 <i>Coan Precognitions</i> , 621.8 |
| “Anaesthetoisi” [αναίσθητοισι] (1) | Noun, dative in plural, derived from the adjective “anaesthetos” [αναίσθητος], in ionic form | <i>Letters</i> , 17th Letter, line 291 |
| “Anaesthetotera” [αναίσθητότερα] (1) | Neuter comparative adjective of “anaesthetos” [αναίσθητος], meaning: less sensitive | <i>Ancient Medicine</i> , 15.25 |

^a In brackets [...] is given the original Greek spelling in the monotonic system, and in brackets (...) the total number of times each word appears.

itemizing the works of all classic authors. The database includes search options for a combined search. For example, a particular word can be sought in a particular work, author, or in all classic literature, and the program automatically provides the number of citations together with the relevant text. Specifically, the words “anaesthesia” [αναίσθησις], ‡ “analgesia” [αναλγησις], and the ancient Greek words Hippocrates used most frequently for pain, such as “algos” [άλγος], “algema” [άλγημα], “odyne” [οδύνη], and “ponos” [πόνος] were sought in all 60 Hippocratic article. In the word search mode, there are options such as “exact word,” “prefix,” “suffix,” and “any.” We used the “any” mode and entered only the prefix of the words to be searched, to find citations that also include words with common roots, compound words, or words stemming from the particular words. For example, we entered the prefix [αναίσθη] for “anaesthesia” related words, and [αλγ], [αναλγ], [οδύνη], and [πόνος] for the words “algos,” “analgesia,” “odyne,” and “ponos,” respectively. The relevant citations were then examined in the original Greek texts and compared with classic English translations.

RESULTS

The word “anaesthesia” and its derivatives appear only 12 times in five Hippocratic texts (Table 1). “Algus,” the ancient word for pain, is also mentioned only 14 times, in contrast to words stemming from it that are very common, appearing 483 times (Table 2). Such words are the verb “algeo” and its derivatives and the very common adjective, still in use, “algeinos,” and compound medical terms such as “kardialgia,”^{6a} “hysteralgia,”^{7a} “cephalgia,”^{8a} and “osphyalgia”^{9a} (Table 3). The contemporary term “analgesia” derived from the words “algos” and “algeo” and the privative prefix “an” does not appear as such in the Hippocratic Collection. Its derivatives, the adjectives “analgetos”^{10a,11a}

and “analgea”¹² appear four times. In contrast to “algos,” a common word for pain in the Hippocratic texts is “odyne” (pain of body and pain of mind),¹³ appearing almost 884 times as such or as a compound word such as the adjectives “epodynos”^{6b} and “anodynos.”^{11b} “Ponos” is also a very common medical term, appearing about 722 times (Table 2).

DISCUSSION

Use of the Word “Anaesthesia” and Its Derivatives by Hippocrates

The search of the articles of the entire Hippocratic Collection revealed that the word “anaesthesia” was first used in a medical context, as loss of consciousness and sensation, by Hippocrates (c. 460–380 BCE). In the work *Breaths*, the word “anaesthetos” (senseless) acquires the medical meaning of loss of sensation, when Hippocrates writes: “For when they [breaths] pass through the flesh and puff it up, the parts of body affected lose the power of feeling [“anaestheta”§]^{10b} (Table 1). It is from the Greek adjective “anaesthetos,” still in use today, that the word “anaesthesia” was derived, in the same way as “analgesia” was derived from the adjective “analgetos” (not sensing pain).² In the same work, “anaesthesia” is related to “analgesia” for the first time, when it is stated that an unconscious patient is also insensitive to pain: “At this time the patients are unconscious [“anaesthetois”§] of everything, deaf to what is spoken, blind to what is happening and insensible to pain [“analgetois”§].”^{10a} However, both words express loss of feeling and pain insensitivity caused by a disease process rather than from a pharmacologic action. Another example described in the work *Epidemics* is the case of a patient who “took no notice [“anaesthetos”]” of his symptoms on the seventeenth day of his fatal disease.^{14a} Again, the loss of consciousness is related to a fatal outcome. It is remarkable how Hippocrates recognizes the consequences of a serious

‡Ancient words using Greek characters and in the monotonic system are given in brackets [...].

§The endings “a,” “oi,” and “ai” indicate plural forms.

Table 2. The Most Frequently Used Words for Pain and Their Derivatives, Their Explanation in English and the Main Works of the Hippocratic Collection Where These Words Appear^a

| Words related to pain | Their derivatives | Explanation in English | Main Hippocratic works in which these words appear |
|--|--|--|--|
| "Algos" [άλγος] (14) | Noun "algema" [ἀλγημα] (194) | Pain felt or caused, suffering | <i>Epidemics</i> (81) <i>Coan Prenotions</i> (88) <i>Prorrheticon</i> (38) |
| | Noun "algedon" [αλγηδών] (13) | Pain, suffering of body or mind, grief | |
| | Adjective "algeinos" [αλγεινός] (2) | Painful, grievous | |
| | Verb "algeo" [αλγέω] (185) | To feel bodily pain, to suffer, to feel pain of mind | |
| | Past participle of the verb algeo "algesas" [αλγήσας] (4) | Smarting with pain | |
| | "Proalgesas" [προαλγήσας], past tense participle of the verb "proalgeo," derived from the preposition "pro" and the verb "algeo" (4) | Feel pain beforehand | |
| | Noun "analgesia" [αναλγησία] derived from the words "algos" and "algeo" and the privative prefix "an" | Absence of sense of pain | |
| | Adjective "analgetos" [ανάλγητος], derived from the privative "an" and "algos" (3) | Free of pain | |
| | Adjective "analgea" [ανάλγεα], derived from the privative "an" and "algos" (1) | Painless | |
| | "Odyne" [οδύνη] (772) | Verb "odynao" [οδυνάω] (51) | |
| Noun "odynema" [οδυνημα] (5) | | Pain | |
| Adjective "odyneros" [οδυνηρός] (2) | | Painful, distressing | |
| Adjective "odynodes" [οδυνώδης] (54) | | Painful | |
| Adjective "epodynos" [επώδυνος], derived from the preposition "epi" and odyne (53) | | Painful | |
| Adjective "anodynos" [ανώδυνος], derived from the privative "an" and odyne (50) | | Painless | |
| "Ponos" [πόνος] (498) | Verb "poneo" [πονέω] (224) | Work hard, suffer, toil in praying, toil in fight, to be busy with, suffer from illness, be sick, work hard at, make or do with pains or care, afflict, distress | <i>Epidemics</i> (112); <i>Aphorisms</i> (28); <i>Coan Prenotions</i> (84) |

^a In brackets [...] is given the original Greek spelling in the monotonic system, and in brackets (...) the total number of times each word appears.

Table 3. Compound Medical Terms of the Word "algos" in the Hippocratic Collection^a

| Compound words from the word "algos" and the verb "algeo" | Derived from | Explanation in English | Main Hippocratic works in which these compound words appear |
|---|---|--------------------------|---|
| "Gonyalgia" [γουνιαλγία] (2) | "Gony" [γόνυ] ^b and the verb "algeo" [αλγέω] | Pain in the knee | <i>Epidemics</i> (2) |
| "Dialges" [διαλγήσ] (1) | The preposition "dia" [δία] and "algos" [άλγος] | Grievous | <i>Diseases I-III</i> (1) |
| "Kardialgia" [καρδιαλγία] (23) | "Kardia" [καρδιά] ^b heart and the verb "algeo" [αλγέω] | Suffering from heartburn | <i>Epidemics</i> (11); <i>Coan Prenotions</i> (8); <i>Prorrheticon</i> (3) |
| "Cephalalgia" [κεφαλαλγία] (63) | "Cefale" [κεφαλή] ^b and the verb "algeo" [αλγέω] | Headache | <i>Coan Prenotions</i> (31); <i>Prorrheticon</i> (16); <i>Epidemics</i> (7) |
| "Osphyalgia" [οσφυαλγία] (6) | "Osphys" [οσφύς] ^b and the verb "algeo" [αλγέω] | Lumbago, back pain | <i>Coan Prenotions</i> (5); <i>Prorrheticon</i> (1) |
| "Hysteralgia" [υστεραλγία] (1) | "Hystera" [υστέρα] ^b and the verb "algeo" [αλγέω] | Pain in the womb | <i>Regimen in Acute diseases</i> (1) |

^a In inverted commas "... " are given the original Greek words in Latin characters, in brackets [...] the same words in Greek characters in the monotonic system, and in brackets (...) the total number of times each word appears.

^b Explanation in English of the prefix words used: "gony" = knee; "kardia" = heart; "cefale" = head; "osphys" [οσφύς] = back; "hystera" [υστέρα] = womb.

illness with a fatal outcome. In *Coan Prenotions*, a patient with inflammation of the lungs and heart is paralyzed ["paraluetai"] completely, lies frozen, and senseless ["anaesthetos"] and eventually dies on the second or third day.^{9b} In the same work, he remarks that any evacuation which takes place without the patient sensing it ["anaesthetos"] is fatal.^{9c}

Another interesting clinical observation of an untoward effect that leads to a coherent and practical suggestion is found in the work *Use of Liquids*. Hippocrates describes the use of warm water as a cure and suggests that the water should not be hotter than the patients can tolerate, "except in cases of loss of speech, paralysis, numbness ["nenarkomenoisin"] or anesthesia ["anaestheta"]," otherwise the doctor may cause burns without realizing it.¹⁵ In these lines, we find the Greek word "nenarkomenoisin" which is a passive perfect participle of the verb "narkoo" (to grow numb), from which "narcosis" is derived, next to the word "anaestheta." In one of his best-known works, *Ancient Medicine*, Hippocrates attributes to inanimate objects, like "a leathern or wooden vessel" the human properties of being "less sensitive ["anaesthetotera"] than man . . ." to the effect of "hot or cold and astringent or insipid" things.¹⁶

Components of Contemporary "Anesthesia" in the Hippocratic Collection

Although Hippocrates does not refer to pharmacologic anesthesia and its different aspects, he knows that some substances can induce sleep. Most interestingly, in *Epidemics* the word "hypnikon" (producing sleep) is found, derived from the word "hypnos" (sleep), from which the contemporary word hypnosis originates.¹³ Hippocratic doctors used the word "hypnikon" to describe soporific substances applied to patients with toothache.^{6c} A related word "hypnoticon," still used in modern Greek, from which the term hypnotic is derived, is found in the work *Diseases of Women* in which Hippocrates refers to "meconium" (opium poppy) as "sleep producing" ["hypnotikon"].¹⁷

Hippocrates in his writings also refers to some fundamental components of contemporary anesthesia, such as airway protection, the state of sleep and the term "narcosis." In one of his best-known works, *Diseases III*, he describes the insertion of narrow tubes into the swollen throat of a patient suffering from "kynanche," the Greek word for quinsy. "With angina ["kynanche"], as it is called, the person chokes and seems to have something like an apple caught in his throat." As a treatment, the author suggests that the doctor "must also clean out the lower cavity with medication or enema, and insert tubes ["avliskoi"] into the throat behind the jaws, in order that air may be drawn into the lung."^{18a} We may assume that these tubes that kept an open airway must have been premature types of a nasopharyngeal airway or even a tracheal tube. In this case, Hippocrates might be the first ancient Greek physician to

manage the airway by bypassing a pharyngeal obstruction and facilitating the airflow into the lungs.

In the Hippocratic work *Coan Prenotions*, the word "narke" (temporary decline or loss of senses and movement), from which the word "narcosis" (state of unconsciousness or drowsiness produced by a drug) was later derived, is used jointly with the word "anaesthesia." In this work, Hippocrates states that when unaccustomed numbness and loss of sensibility, "narkai . . . and anesthetai," are present in a patient suffering from strangulating ileus, this is a warning sign of "apoplexy."^{2,9d} In *Aphorisms*, "narke" is also used to describe physical "numbness" and also "dullness of intelligence."^{19a,b}

The philosophical issue of sleep was explored extensively by ancient Greek scholars including Aristotle. Hippocrates approached the issue from the physiologist's perspective. He had noticed that during sleep the body cannot perceive external stimuli, and it is the soul, the contemporary subconscious state, which not only keeps its functions but also even takes over those of the body. In the work *Dreams*, he clearly differentiates the state of sleep from the waking state: "The body when asleep has no perception; but the soul when awake has cognizance of all things, sees what is visible, hears what audible, walks, touches, feels pain, ponders. In a word, all the functions of the body and of soul are performed by the soul during sleep."²⁰ However, he only refers to natural sleep and not pharmacologic sleep. This can be explained by his opposition to surgery, which he left to other practitioners. The Hippocratic Oath unambiguously states: "I will not use the knife, not even, verily, on sufferers from stone, but I will give place to such as be craftsmen therein."²¹ This interdiction against the knife explains why in the Hippocratic Collection there is not a single reference to the use of soporific plants or opium to calm the acute pain of surgery. However, Hippocrates must have known the properties of those substances and often used them for the treatment of pain, as we will see later.

Even though Hippocrates did not describe anesthesia with the word "anaesthesia" as it is defined today, he was the first to use this word in a medical context to describe loss of consciousness and sensation. Five centuries later, Dioskourides used this word to describe the absence of sensation caused by drugs.¹ Finally, more than 2000 years after Hippocrates, Oliver Wendell Holmes in a moment of inspiration, very accurately, used this word to describe a state closer to the modern definition and understanding of clinical anesthesia.

The Vocabulary of Pain in the Hippocratic Collection

Hippocratic physicians developed a rich vocabulary for pain in which the physical and moral elements overlap. There are numerous citations throughout the Hippocratic Collection describing and differentiating between painful conditions. The words and their derivatives most frequently used by Hippocrates are "algos," "algema," "odyne," and "ponos" (Table 2).

Table 4. Adjectives Describing the Different Types of Pain in the Hippocratic Collection and Their Explanation in English^a

| Adjectives for pain | Explanation in English | Main Hippocratic works in which these adjectives for pain appear |
|-----------------------------------|--|--|
| "Deine" [δεινή] "odyne" | Fearful, terrible pain | <i>Epidemics</i> (book 7, section 5) |
| "Ischyri" [ισχυρή] "odyne" | Powerful, forcible, violent, severe pain | <i>Epidemics</i> (book 2, section 5, paragraph 2); <i>Internal Affections</i> (section 14) |
| "Karebarike" [καρηβαρική] "odyne" | Pain causing heavy head | <i>Epidemics</i> (book 3, chapter 3, case XII); <i>Coan Prenotions</i> (section 164) |
| "Oxeia" [οξεία] "odyne" | Acute, sharp pain | <i>Coan Prenotions</i> (section 514); <i>Internal Affections</i> (section 28) |
| "Sphodros" [σφοδρός] "ponos" | Vehement, violent, excessive, severe pain | <i>Regimen in Acute Diseases</i> (Appendix, section 55) |
| "Psychrai" [ψυχραι] "odynae" | Cold pain, in the sense of old and chronic | <i>Epidemics</i> (book 6, section 1, paragraph 7) |
| "Thermai" [θερμαί] "odynae" | Warm pain, in the sense of recent | <i>Epidemics</i> (book 6, section 1, paragraph 7) |

^a In brackets ". . ." are given the original Greek words in Latin characters, in [. . .] the same words in Greek spelling in the monotonic system and in (. . .) a specific citation for each work.

Some of them, still in use in modern Greek, are also found as loans in compound words in other languages. In the Hippocratic Collection, "algos" represents a more general type of suffering involving the whole body, which is prolonged and susceptible to recurrence.²² The word "algema," like "algos," is used for a more general type of pain, such as "chronic pain in the loins," "pains of the forearms and the neck," or even to differentiate between types of headache.^{8b-d} "Odyne" describes acute, sharp, and localized pain and intense mental pain.^{2,22} In *Epidemics* "odyne" is used to explain "pain in the left ribs"^{6d} or "pain in the right hypochondrium."^{14b} The compound word "epodynos" (painful) is used to describe painful areas of the body like a "painful sprain behind the thumb."^{6b} "Ponos," the modern Greek word for pain, originally meant labor and hard work in the Homeric epics. This meaning may have originated from the personification of "Ponos" (Toil) and "Algea" (Sorrows) as children of the hard-hearted goddess "Eris" (Strife) in Greek mythology.²³ Much later, the consequences of labor or distress were described as "ponos" in which case it meant physical pain.²⁴ However, it was Hippocrates who used the word to describe the physical pain caused by disease, such as pain in the joints.^{19c} "Ponos," like "algos" describes a more general type of pain (Table 1), for example, "heaviness in the bowels with pain," "painful, continuous, acute fever," or "chronic and painful, watery inflammations of the eyes."^{14c}

The Significance of Pain as a Diagnostic and Prognostic Tool

Hippocrates was the first physician to rationalize pain and use it as a valuable diagnostic and prognostic tool. He considered pain in relation to the overall clinical picture of the patient and not as an isolated symptom. He used the clinical features of pain as important manifestations in the disease process and as a major tool to outline the prognosis and severity of an illness. Numerous citations throughout the Hippocratic texts testify to this. For example, Hippocrates noted the time when the pain starts, to elucidate the

course of the pathogenic process: ". . . pains and fevers occur when pus is forming rather than when it has been formed"^{19d} or, in the case of consumption in the *Epidemics*, "in the majority of these cases the throat was painful throughout from the beginning"^{14d} When two different, distinct pains occurred simultaneously, he related the most intense one to the more serious illness: "when two pains occur together, but not in the same place, the more violent obscures the other."^{19e} The anatomical location of the pain was an important diagnostic sign. In *Prognostics*, for example, pain accompanied by tachypnea indicated ailments in the chest: "rapid respiration indicates pain or inflammation in the parts above the diaphragm."^{25a} Also, in *Aphorisms* it is pointed out that "pains and swellings of the belly are less serious when superficial, more severe when deep-seated."^{19f} Specific features of pain, such as duration, intensity, location, or depth, were sought and scrutinized to determine the fatality or seriousness of a disease: "Violent and continuous headaches, should there be in addition one of the deadly signs, is a very fatal symptom . . ."^{25b} or "pains occurring with fever in the region of the loins and lower parts, if they leave the lower parts and attack the diaphragm, are very mortal."^{25c}

To explain, emphasize or differentiate among the different manifestations of pain, Hippocrates complements these terms with precise adjectives, such as "oxeia odyne,"^{25d} or "ischyros ponos"^{14e} (Table 4).

Nonpharmacologic and Pharmacologic Cures for Painful Conditions in the Hippocratic Texts

In the Hippocratic Collection, many different non-pharmacologic cures for painful conditions are described, such as diet, heat, cold, ablution, purging, cauterization, expectoration, venesection, incisions for pleurisies, or hot effusions for headaches. Some of them are quite bizarre by modern medical standards. For example, in the *Aphorisms*, the opening of a vein, "phlebotomy" (venesection), was suggested for curing headaches: "Pains at the back of the head are relieved by opening the upright vein in the forehead."^{19g} Again, in a patient with delirium and "aphonia" (loss of voice)

who suffered from pains in the heart, "phlebotomy stopped these pains."^{6e} For gastrointestinal pains, a common treatment was purging. "Pains above the diaphragm indicate a need for upward purging; pains below indicate a need for downward purging."^{19h} Rest plays a major role in the relief of pain: "In every movement of the body, to rest at once when pain begins relieves the suffering."¹⁹ⁱ

In certain sections of the Hippocratic work great emphasis is placed on therapies in which opposites cure opposites and like curing like. In *Places in Man*, it is explained that "pains are cured by opposites." In the same passage it is stated that, "sometimes conditions can be treated by things opposite to those from which they arose, and sometimes by things like to those from which they arose."^{26a} It is worth wondering whether these observations were the forerunner of later discoveries about activation or deactivation of facilitating or inhibiting mechanisms during nociception.

In addition to nonpharmacologic cures, Hippocratic physicians also used the different properties of various substances. In *Places in Man*, it is clearly stated that "all substances that change the state of a patient are medications ['pharmaka']."^{26b} In the Hippocratic Collection, 236 distinct plants are mentioned. Most of them have soporific, narcotic, or poisonous properties, such as mandrake, henbane (*Hyoscyamus*), nightshade, and especially poppy.²⁷ In the work *Fistulas*, it is suggested that a patient with anal inflammation and protrusion should "drink white meconium" (white poppy) if the pain does not subside by other means.²⁸ In *Diseases III*, for pain in the hypochondrium due to pleurisy, it is suggested to give the patient white opium poppy to drink with other substances, such as "cumin, flower of copper, honey, vinegar, water" and others.^{18b} The opium extracts in the Hippocratic texts were mainly prescribed for painful gynecological ailments.^{29,30} Other substances used for the same painful conditions include silphium (a sort of asafetida),³⁰ cumin with honey, leek,³⁰ cyclamen,³⁰ and many others. In *Regimen in Acute Diseases*, the author suggests the use of black hellebore (*Helleborus niger*) and peplium (*Euphorbia peplus* or petty spurge) as purgatives that stop the pain, in combination with daucus (*Athamanta cretensis*), seseli (*Laserpitium latifolium* or laserwort), anise, and juice of silphium.^{7b}

CONCLUSIONS

The study of the Hippocratic Collection in the original Greek language revealed Hippocrates as the first physician to use the words "anaesthesia" and "analgesia" in a medical context. His realistic approach to health and healing led to important observations on fundamental components of contemporary anesthesia, such as the state of sleep and narcosis and also sleep-inducing substances. In the Hippocratic texts, analgesia is related to anesthesia for the first time, when it is pointed out that an unconscious

patient is insensitive to pain. Hippocrates may have been the first physician to keep an open airway and facilitate airflow to the lungs by bypassing an inflammatory obstruction of a patient's throat with the insertion of a premature type of oropharyngeal airway or, probably, tracheal tube.

Hippocrates and his followers rationalized pain and defined its various characteristics, such as location, duration, and relation to other symptoms. To elucidate a disease process, they developed a wide pain vocabulary, still in use today. Pain was developed as a diagnostic and prognostic tool to help differentiate between various painful conditions. According to the Hippocratic writings, the therapeutic approach to painful conditions included diverse, sometimes bizarre, nonpharmacologic, and pharmacologic cures. The opium poppy was one of them, but it was also used as a "sleep-inducing" substance.

The rational clinical observations of Hippocrates freed medicine from religion and laid the ground for the development of medicine as a systematic science. The wealth of medical knowledge found in the Hippocratic writings explains why he is considered the father of modern medicine.

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Elton Romeo Smilie, the Not-Quite Discoverer of Ether Anesthesia

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Like William T.G. Morton, Elton Romeo Smilie (1819–1889) was raised in Massachusetts, attended medical school in New England, practiced dentistry there, strove for clinical invention, and moved to Boston. In October 1846, both announced that inhaled ethereal preparations achieved reversible insensibility in surgical patients. Smilie published¹ a report in the *Boston Med Surg J* 3 wk before Bigelow used that forum to broadcast Morton's Ether Day. Smilie's preparation was an ethereal tincture of opium, and, as he mistakenly believed the opium to be volatile and important, he ceded priority to Morton for ether anesthesia. The two authors collaborated on chloroform, but Smilie soon headed off in the Gold Rush to California. It is tempting to speculate that Charles T. Jackson and Morton were indebted in part to Smilie.

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“**E**ther Day” at the Massachusetts General Hospital is officially October 16 when, in 1846, William T.G. Morton administered inhaled “Letheon” to a patient of surgeon John C. Warren.¹ An alternative anniversary date, November 7, was the day that Morton revealed to Warren that the only active ingredient of Letheon was diethyl ether.² “Beating his professor into print,” 28-year-old Bigelow³ published an account of October 16 in the *Boston Med Surg J* on November 18. Warren's own article appeared on December 9.⁴

Before both of those articles, another Boston surgeon independently published his own work on inhaled ether in the same journal on October 28.^{1,5} The letter came from Elton Romeo Smilie. Smilie came close to the discovery of inhaled ether for surgery, but he did not quite do so. He interestingly timed but misinterpreted that ether experiment is fascinating in the history of medical science. Unfortunately, little information has been collected about the person. McMechan⁶ pointed out this historical omission in 1915 in a letter requesting information about Smilie from *Boston Med Surg J*. Unfortunately, the response was only a reprint of Smilie's letter of 1846. The first historian to report investigation into Smilie's biography was probably Wolfe¹ in 2001.

Smilie obtained excellent surgical insensibility in patients by having them supposedly inhale opium.

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Although opium can be smoked, its pharmacological components are not volatile at room temperature or slightly higher. He mistakenly believed that he rendered the opium volatile by mixing it with a volatile liquid. The liquid he chose was diethyl ether. He published his experiences with inhaled ethereal tincture of opium without testing the diethyl ether alone. A controlled experiment would have changed the history of anesthesia.

It is interesting to wonder who might have known of Smilie's work before its publication. Warren, for instance, had previously been the editor of the journal. However, it is unlikely that Warren had been tipped off about ether because of Smilie. If anything, Smilie's article may have helped Morton to inadvertently conceal the active ingredient of Letheon from Warren.² That is, Smilie's report suggested that additives were also required for Morton's ethereal nostrum to work.

ELTON ROMEO SMILIE (1819–1889)

He was born in Wakefield, Massachusetts, to John and Priscilla Smilie on August 17, 1819, the same year that Morton was born 60 miles away.⁷ In 1842, he received the degree of Doctor in Medicine from Vermont's Castleton Medical College, one of the largest American medical schools of the mid-1800s. Tooth extraction was the most common surgical procedure at that time, and his dissertation was entitled “Structure and Diseases of the Teeth.”⁸ He started his practice in Derry, New Hampshire, hometown of his wife, Mary Ann Hall⁹ and quickly established a reputation for creativity.^{10–27}

In his first article on ether, a “cold ethereal solution of opium” was placed in a glass retort.⁵ “Moderate heat” was applied to cause “slow evaporation,” “the patient being permitted to breathe the gaseous vapor

from an elastic tube fixed to the mouth of the retort." The surgeries were not specified, but "there was an entire absence of symptoms induced by pain, and those which usually result from the excessive use of opium." The onset was instantaneous, and ether was, beyond doubt, the best vehicle for the introduction of opium into the system. Somehow, "the dose depends on the judgment of the physician." As ether boils at 35°C, warming the ether produced a potentially high dose of ether vapor.

Smilie made three incorrect assumptions. The first was that narcotic components of opium are soluble in ether. The second was that dissolved opium would vaporize when its solvent vaporized and thus be contained in the fumes of diethyl ether. The third, and most important, was that the intended carrier vapor had no intoxicating properties. Contrary information was available at the time of Smilie's experiments. It was known that the two most abundant alkaloids of opium are morphine and narcotine. Both were extractable into water, from which nonvolatile morphine had been crystallized. When opium was mixed with ether, the ether took up narcotine but not morphine.²⁸ Despite its name, narcotine (now called noscapine) is not a narcotic. Although narcotine dissolves in ether, ether does not promote the evaporation of narcotine. It was known that after ether leaves an ethereal tincture of opium, solid narcotine (melting point 176°C) remains.²⁸

Smilie's²⁹ second article on ether appeared on May 5, 1847, after both the Bigelow and Warren accounts of Morton's Ether Day. He ceded credit for the invention of ether anesthesia to Jackson and Morton. He wrote, "I trust that I shall not be accounted by the profession and public, one of those parasitic growths, which by extent of foliage seemingly endeavor to conceal the connection of fruit with the legitimate branch." He explained that his independent work began in the spring of 1846, when he constructed "an instrument for inhaling medicinal vapors in pulmonary complaints." The first patient to receive ethereal tincture of opium was a clergyman "suffering from extensive bronchial irritation." Left alone during his treatment, the patient became unconscious and "fell upon the floor, severely injuring his head against the projecting corner of the stove." Fortunately, the patient found the mishap "far from unpleasant." The next patient was a young lady suffering from pain and cough due to tuberculosis. She would not relinquish the therapeutic ether inhaler to Smilie until her insensibility ensued, but then she was easily resuscitated with the aid of salts of ammonia. The third patient was deliberately rendered insensible for the draining of a large abscess involving the neck and chest.

The last paragraph of Smilie's²⁹ note of May 1847 is unclear. After giving ether to "hundreds of patients," he said that he suspended his ether experiments until August 1846. He and his consultants arbitrarily feared that the tincture was potentially injurious, perhaps because of the possibility of opium-induced apnea. He

resumed the administration of the drug "with the assurance guaranteed by the experiments of Dr. Morton." Thus, there is a suggestion that Smilie and Morton communicated about ether in August before Ether Day in October 1846.

Smilie³⁰ reiterated his concession of the invention of ether anesthesia to Jackson and Morton in a lecture to his medical school. However, not everyone felt that the concession was entirely fair. For instance, Flagg,³¹ a student of Warren, argued strenuously against the Morton-Jackson legal patent on ether anesthesia. He said that it was like a patent on sunlight and pointed out that Smilie had demonstrated the power of Morton's supposedly "new gas." (Interestingly, Flagg mentioned that he himself had given ether as an oral or inhaled drug to "hundreds" of patients, although he did not claim its use as an aid to surgery.) Dr. John Clough of Boston was compelled to write that Smilie had told him, in the spring of 1846, about insensibility from inhaled ethereal tincture. According to Clough,³² "It is true that Dr. S. had used the ether, to be inhaled, for some purposes, and had suggested the use of it in the same way for overcoming pain while dental operations were being performed, before it was made public by Dr. Morton." An anonymous note signed by "Justice" chided Bigelow for claiming the first public article on etherization. Justice credited Smilie and mentioned that Smilie's article of October 28, 1846, had been reprinted in the *Edinburgh Med Surg J*.³³

Smilie remained on friendly terms with Morton, and he helped Morton to examine chloroform anesthesia. Morton³⁴ explained, "... being out of health myself, I called upon Dr. E. R. Smilie, a person of some reputation in chemical science, and invited him to my laboratory." Smilie helped Morton with his first chloroform patient and then invented an improved inhaler for ether or chloroform. As described, "The mouth piece is of glass, and is connected with the receiver by a silver tube, within which are the valves that prevent the passage of the breath from the lungs into the retort, and allow of its escape."³⁵ "Like Connecticut washing machines," there was a plethora of types of chloroform inhalers put forth, but the Smilie device garnered a good review.³⁶ Unfortunately, there is no image of Smilie's non-rebreathing valve system of 1848. The dangers of chloroform were often ascribed to impurities, so Smilie,³⁷ having communicated with James Y. Simpson, published Simpson's recipe for a "superior article" in Boston.

Smilie enjoyed a sterling reputation. In 1849, the Philadelphia College of Medicine conferred on him the courtesy (*ad eundem*) degree of Doctor of Medicine. He was then admitted into the Massachusetts Medical Society.³⁸

On January 30, 1850, it was announced in the *Boston Med Surg J* "Dr. E. R. Smilie, a frequent contributor to this Journal, who has invented several novel and approved surgical instruments, sailed from Boston to California, a few weeks since."³⁹ He went to the Gold Rush. His preparations included the invention of an

apparatus for isolating particles of gold from sand (www.rcsed.ac.uk/site/PID=2312004161515/761/default.aspx).

Smilie wrote of dentistry and medicine while in California. One of his case reports exemplifies the California Gold Rush literary license.⁴⁰ He describes a 49er whose hair turned white overnight. The man was bled for a fever and lapsed into sleep. The rapid blanching of his hair was supposedly caused by his awakening to a grizzly bear lapping up the spilled blood.

Smilie^{41,42} had many stories to tell, and he penned two science fantasy novels. He is considered a fore-runner of H. Rider Haggard and Edgar R. Burroughs and a pioneer of the genre (www.erbzine.com/mag18/soong.htm). As R. Elton Smilie, he published *The Manatitlans*. Therein, despite dangerous ape-men and other hazards, Andean explorers discovered a lost world of ant-sized people. Next was *Investigations and Experience of M. Shawtinback, at Saar Soog, Sumatra*. Humans in that novel were improved surgically to a nobler state of health resembling those enjoyed in Eden. The improvement was affected by the transplantation of anatomically correct monkey tails onto the humans. The surgery required, of course, an “anesthetic.” To that end, the inventor of “ethereal tincture of opium” invented “etherial [*sic*] tincture of bang”⁴² where bang is an inebriating hemp product.

CONCLUDING REMARKS

It is interesting to speculate as to who read the Smilie’s article on ether before its publication. Warren was the inaugural editor of the first incarnation of the journal. In 1846, the editor was Jerome V.C. Smith. Smith had many personal connections (and went on to become the mayor of Boston). A professional chemist such as Jackson should have seen Smilie’s misinterpretation at a glance. Whether or not Smilie’s manuscript tipped off the producers of Ether Day, his publications show that ether anesthesia was about to happen anyway. The other pioneers of inhaled anesthesia were colorful characters, and Smilie certainly shared that characteristic. Alas, no visual image of the person seems to have been preserved.

William Clarke used ether for dental extraction before Morton,⁴³ Crawford Long used ether for surgery before Morton, and Smilie published before Morton. Alas, Clarke and Long did not publish before Ether Day, and Smilie did not quite get the idea correctly.

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CME Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Trial

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BACKGROUND: Despite the enormous success of total knee arthroplasty (TKA), chronic neuropathic pain can develop postoperatively and is both distressing and difficult to treat once established. We hypothesized that perioperative treatment with pregabalin, a chronic pain medication, would reduce the incidence of postsurgical neuropathic pain.

METHODS: We performed a randomized, placebo-controlled, double-blind trial of pregabalin (300 mg) administered before TKA and for 14 days after TKA (150–50 mg twice daily). Patients were screened for the presence of neuropathic pain at 3 and 6 mo postoperatively using the Leeds Assessment of Neuropathic Symptoms and Signs scale. Secondary outcomes included postsurgical recovery and rehabilitation measures, including knee range of motion, opioid consumption, postoperative pain scores, sleep disturbance, and time to discharge as well as the occurrence of postoperative systemic complications.

RESULTS: Of the 240 patients randomly assigned to the 2 treatment groups (120 in each), data for the primary outcome were obtained from 113 pregabalin patients and 115 placebo patients. At both 3 and 6 mo postoperatively, the incidence of neuropathic pain was less frequent in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 and 6 mo, respectively; $P = 0.001$ and $P = 0.014$). Patients receiving pregabalin also consumed less epidural opioids ($P = 0.003$), required less oral opioid pain medication while hospitalized ($P = 0.005$), and had greater active flexion over the first 30 postoperative days ($P = 0.013$). There were no differences in the actual recorded duration of hospitalization between the 2 groups, although time to achieve hospital discharge criteria was longer for placebo patients, 69.0 ± 16.0 h (mean \pm SD), than that of pregabalin patients, 60.2 ± 15.8 h ($P = 0.001$). Sedation ($P = 0.005$) and confusion ($P = 0.013$) were more frequent on the day of surgery and postoperative day 1 in patients receiving pregabalin.

CONCLUSION: Perioperative pregabalin administration reduces the incidence of chronic neuropathic pain after TKA, with less opioid consumption and better range of motion during the first 30 days of rehabilitation. However, in the doses tested, it is associated with a higher risk of early postoperative sedation and confusion.

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Osteoarthritis currently affects approximately 27 million adults in the United States and is expected to increase by the year 2030.¹ The sequelae of arthritis, such as pain and disability, frequently necessitates joint replacement surgery. Total knee arthroplasty (TKA) is a highly effective treatment for end-stage knee osteoarthritis, and correspondingly, these procedures are increasing

both in the United States and globally. In the United States alone, 550,000 TKAs were performed in 2007.²

Despite advances in surgical technology and perioperative anesthetic management, the incidence of chronic neuropathic pain after TKA surgery has not decreased³ and is as high as 12.7% at 6 mo postoperatively.⁴ Neuropathic pain is a distressing condition that is characterized by allodynia, hyperalgesia, edema, and skin color changes of the limb. Treatment of neuropathic pain is often both challenging and prolonged, with substantially diminished quality of life. Gabapentin and the related more potent compound pregabalin have been shown to be beneficial in the treatment of neuropathic pain.^{5–7} Because of the chronic and distressing nature of neuropathic pain, as well as the difficulty in treatment and resolution, preventing development of this syndrome is highly advantageous.

Pregabalin given before surgery has been shown to reduce dental pain after molar extraction,⁸ reduce

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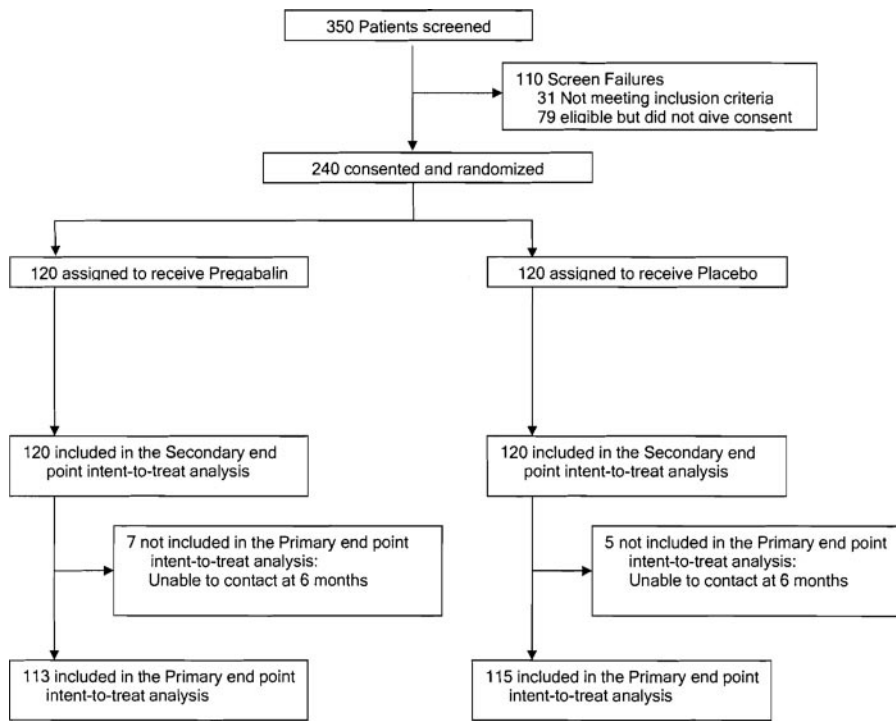


Figure 1. CONSORT flow chart of study.

postoperative morphine requirements after total hip arthroplasty,⁹ and attenuate postoperative pain after laparoscopic cholecystectomy¹⁰; however, other studies show no beneficial effect of pregabalin on acute postoperative pain when administered preoperatively for minor gynecological surgery,¹¹ elective ambulatory and short-stay surgery,¹² and laparoscopic cholecystectomy.¹³ However, no clinical study has yet investigated whether perioperative administration of pregabalin can reduce the incidence of postoperative chronic neuropathic pain. The primary objective of this study was to evaluate whether pregabalin given before and for 14 days after TKA reduces the incidence of neuropathic pain assessed at 6 mo postoperatively. Secondary outcomes assessed include knee range of motion (ROM), acute postoperative opioid requirements, and time until hospital discharge criteria is achieved.

METHODS

After receiving IRB approval, from August 2006 to August 2007, 350 consecutive patients scheduled to undergo elective primary TKA were contacted and assessed for study eligibility (Fig. 1). Written informed consent was obtained from each patient. Two hundred forty patients undergoing primary TKA were enrolled in this randomized, placebo-controlled, double-blind trial. Patients were randomized to a treatment group using a computer-generated randomization sequence. This study was approved for a physician-sponsored investigational new drug (IND) No. 72,121 issued (January 2006) by the Food and Drug Administration (FDA).

Inclusion/Exclusion Criteria

Patients were eligible for the study if they were scheduled to undergo a primary TKA with a diagnosis

of osteoarthritis of the operative knee and had the ability to understand and read English. Patients were excluded if they were younger than 21 yr or older than 80 yr; had an ASA physical status of IV; had prior use of gabapentin (or pregabalin) or nonsteroidal antiinflammatory drugs (NSAIDs) within 2 wk before surgery; had a history of neuropathic pain or any other chronic pain condition, other than osteoarthritis pain; were pregnant; had a sulfa allergy; or were currently enrolled in another investigational study.

Treatment Protocol

Patients were randomly assigned (SAS Statistical Software 9.1.3) to receive either the study medication or placebo. There was no dose administered on the days before surgery. Patients randomized to the experimental arm of the study received pregabalin 300 mg orally (*per os* [PO]), 1–2 h before surgery, 150 mg twice daily for the first 10 postoperative days, 75 mg twice daily on Days 11 and 12, and 50 mg twice daily on Days 13 and 14. Pregabalin is not approved by the FDA for perioperative use, and therefore, the primary investigator consulted with the FDA before commencing the study. Dosing was approved in the physician-sponsored IND No. 72,121 by the FDA. Although this is an off-label use of the study drug, the doses do not exceed the daily limit allowed for the treatment of chronic pain. Control patients received PO-matched placebo tablets, at identical time points, with both pregabalin and placebo capsules provided by Pfizer (New York, NY). After discharge, patients were provided with diaries in which they recorded the exact times at which they took pregabalin/placebo each day. All patients were contacted 1 wk after their discharge via a phone call to ensure their compliance with the study

medication. They were asked to return any unused drug, along with the diaries, at their 1-mo visit to the surgeon's office. The physicians and nurses managing the patient perioperatively, the personnel involved with postoperative pain assessments and management of the epidural infusion, physical therapists, and the study patients were blinded to group assignments. During the study, only the dispensing pharmacist had knowledge of the study codes. Pfizer, the manufacturer and provider of pregabalin and placebo, was not involved in protocol development, data collection and management, statistical analysis, or manuscript preparation.

In the operating room, patients were sedated with midazolam, and a combined spinal-epidural anesthetic was used for the operation as previously described.¹⁴ After obtaining clear cerebrospinal fluid, 1.5 mL of 0.75% hyperbaric bupivacaine with 25 μ g of fentanyl was injected. After the intrathecal injection, a catheter was inserted for epidural drug administration. Patients were sedated with IV propofol for the duration of the surgery. At the completion of surgery, an epidural infusion of fentanyl (5 μ g/mL) and bupivacaine (1 mg/mL) was initiated using a continuous basal infusion of 6 mL/h with superimposed patient-controlled epidural analgesia (PCEA) bolus doses. Patients were instructed before surgery to use the PCEA mode, so as to maintain their pain score (at rest) between 2 and 4 on the 11-point numerical rating scale (NRS), where 0 = no pain and 10 = worst possible pain. If the pain scores could not be maintained (NRS \geq 4 and the maximum number of PCEA boluses was used¹⁴), the basal infusion rate was increased while maintaining the PCEA mode. However, the maximum amount of epidural solution that could be used per hour was 10 mL. The epidural infusion was discontinued between 32 and 42 h postoperatively. Patients were then transitioned to oral opioid medications (morphine, oxycodone, and hydromorphone) as needed for adequate pain control (NRS < 4). All patients received preoperative celecoxib 400 mg orally, 1–2 h before surgery and 200 mg PO twice daily for 3 days while in the hospital, to conform to the multimodal analgesia protocol used at our facility.¹⁵

Surgery

Prophylactic antibiotics (cefazolin IV or vancomycin IV) were administered to all patients before the skin incision. TKA was performed under tourniquet control, using an abbreviated medial parapatellar approach with the arthrotomy extending into the quadriceps tendon for 2–4 cm above the superior pole of the patella, and without patellar eversion. A primary, cruciate retaining TKA was performed in all cases (NexGen CR, Zimmer, Warsaw, IN); all components were cemented, and the patella was resurfaced in all cases. At the time of capsular closure, 60 mL of 0.25% bupivacaine with epinephrine was infiltrated into the wound. The knee was closed in 90° of flexion over a nonrefusion drain (Hemovac, Zimmer Snyder, Warsaw, IN). The drain was

discontinued on postoperative day 1, and patients were started on a physical therapy program that included weight bearing as tolerated and ROM exercises as guided by a physical therapist.

Outcome Measures

Adverse Events

Based on the package labeling for pregabalin, the occurrence of sedation, confusion, dizziness, headache, dry mouth, peripheral edema, and diplopia were assessed daily during hospitalization. In addition, occurrences of postoperative nausea and vomiting and pruritus were recorded based on answers to standardized questions in the morning and evening each day during hospitalization. Patients with postoperative nausea and vomiting were treated with metoclopramide (10 mg) or ondansetron (4 mg) if needed. Adverse events data after hospitalization were supplemented by the surgeon's clinical records up to the 6-mo patient visit.

Chronic Neuropathic Pain and Related Outcomes

Patients were evaluated in a blinded fashion for lower extremity neuropathic pain at 3 and 6 mo after TKA using a measure administered during a telephone interview. The 3- to 6-mo time points are often used to define when acute postsurgical pain becomes chronic pain.³ During this time period, there were no restrictions on patients' use of analgesic drugs. Clinical symptoms of neuropathic pain were assessed, using the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS), to determine the presence of neuropathic pain in the operated leg at each time point (3 and 6 mo postoperatively). S-LANSS is a validated, weighted 7-item assessment tool for neuropathic pain (yes or no for each pain measure) with a maximum score of 24.¹⁶ An S-LANSS score of 12 or more was an indication of chronic neuropathic pain. The 7 variables included 2 self-examination items: allodynia (assessed by gentle rubbing of the operated leg) and hyperalgesia (gently applied pressure from the fingertip); and 5 pain symptoms: pins and needles, skin color change, sensitivity to touch, sudden bursts of pain, and burning. Patients with an S-LANSS score of 12 or more at 6 mo came to the physician's office for a standardized physical examination, which included the S-LANSS examination items (allodynia and hyperalgesia) directly assessed by the physician, plus a pinprick evaluation (physician applying pin to painful area and comparing it to a nonpainful area and recording an increased response in the painful area versus control area). Presurgery NRS scores were obtained from the orthopedic presurgery office visit. To account for concomitant analgesic use in the 6-mo postsurgery period, we reviewed the records of patients from postsurgery orthopedic office visits, up to 6 mo.

In addition, for those patients who were identified with neuropathic pain of the operative knee at 6 mo, knee function was quantified using the validated Knee

injury and Osteoarthritis Outcome Score–Physical function Short-form (KOOS-PS).¹⁷ Comparisons of knee function were made between patients with chronic postoperative neuropathic knee pain, case matched by age and surgeon, with 2 sets of patients without chronic pain, 1 from the pregabalin and the other from the placebo groups, using a random selection. Using the KOOS-PS, patients ranked each of the following 7 variables as to the degree of difficulty, from none to extreme (point values: 0–4): rising from bed; putting on socks/stockings; rising from sitting; bending to the floor; twisting/pivoting on the affected knee; kneeling; and squatting. The raw summed score from the KOOS-PS was then converted to a 0–100 scale, Rasch-based person score.¹⁷

Range of Motion

The degree of active (patient moving the knee) and passive (movement of the knee with the aid of a physical therapist) knee flexion, measured using a goniometer,^{14,18} tolerated by the patient on postoperative days 1–3 was recorded by the physical therapist twice daily, and the maximum daily measure was used for analysis. Follow-up active ROM was assessed at 1 mo postoperatively by orthopedic nurses blinded to the study codes.

Epidural Drug Use and Postoperative Pain Assessment

Epidural medication consumption was recorded for each 4-h interval from the completion of surgery to the time that the epidural was discontinued (same as the time to achieve hospital discharge criteria). Because the discontinuation time varied from patient to patient (as they achieved physical therapy criteria), the average hourly consumption (total analgesic used divided by the total infusion time) was used as the measure of epidural drug use. Pain scores at rest were assessed with the NRS rating every 8 h during the immediate postoperative phase (the first 32–42 h after surgery). All other oral opioid consumption during the entire hospital stay (mainly after epidural infusion was terminated and also during epidural infusion if needed for breakthrough pain) was recorded and subsequently converted to parenteral morphine equivalents for statistical comparisons.

Discharge Time Criteria

The time to achieve hospital discharge criteria (physical therapist appraisal of minimal assistance needed for ambulation; hemodynamically stable; stable cardiac rhythm; noninfected incisions and afebrile patient; and ability to void) was determined.¹⁹

Sleep Interference

Starting from the morning after surgery until hospital discharge, patients were asked daily to rate sleep interference during the previous night on an 11-point scale (0 = no sleep disturbance and 10 = greatest sleep disturbance).¹⁴ The time of the day (between 7 and 9 AM)

at which this assessment was made was kept consistent for all patients on each day of their hospital stay.

Statistical Analysis

The primary hypothesis of reduction in the incidence of neuropathic pain for the pregabalin treatment group compared with placebo was tested by assessing the incidence of neuropathic pain at 6 mo after TKA. An intent-to-treat analysis was applied to all patients consented and randomized for primary and secondary outcomes. A power analysis was performed to determine the sample size required to show a 75% reduction in the incidence of neuropathic pain at 6 mo postoperatively; the published 12.7% incidence of neuropathic pain after TKA⁴ was set as the control value. By using SAS Statistical Software, we determined that for $\alpha = 0.05$ and 80% power, using the Pearson χ^2 1-tailed test for 2 proportions, this required 97 patients in each treatment group. Anticipating that a moderate number of patients would be withdrawn from the study after randomization and the prolonged follow-up time period, we chose 240 patients as our enrollment target.

Demographic and intraoperative data were analyzed with the Student's *t*-test, χ^2 test, or Mann-Whitney-Wilcoxon test as appropriate. Descriptive statistics are reported as mean and SD for continuous variables, median and interquartile range for ordinal variables, and count and/or percentages (%) for dichotomous variables. Unless stated otherwise, results are mean \pm SD. All statistical models were evaluated for assumption deviations and corrected as necessary. Epidural analgesic consumption rate, supplemental postoperative opioid use, KOOS-SP knee score, and time for patients to achieve hospital discharge criteria were compared between the 2 groups using the 2-sample Student's *t*-test. All repeated measurement outcomes (active ROM, passive ROM, and sleep interference) were analyzed with a mixed procedure repeated-measures model with an autoregressive covariance structure, estimated using the maximum likelihood method. NRS pain scores over a postoperative period up to 42 h were analyzed, after verifying that <20% of the scores were 0, as a repeated measurement outcome and evaluating the distributional assumptions. Although the mixed models used are robust against violations of nonnormality, when distributional violations were identified, nonparametric methods were used to confirm parametric results. The incidence of neuropathic pain (S-LANSS ≥ 12), allodynia, or hyperalgesia at 3 and 6 mo, and adverse events were analyzed by χ^2 test and confirmed with exact methods.

RESULTS

Two hundred forty patients were randomly assigned to the 2 treatment groups, with 120 per group (Fig. 1). All patients received the preoperative dose, pregabalin or placebo, and all patients were therefore included in the

Table 1. Patient Demographics and Surgical Data

| | Pregabalin (N = 120) Mean (SD) | Placebo (N = 120) Mean (SD) | P |
|--------------------------------------|--------------------------------------|-----------------------------------|--------------------|
| Age (yr) | 64.0 (8.3) | 63.3 (8.9) | 0.579 |
| Body mass index (kg/m ²) | 34.2 (8.4) | 34.6 (7.7) | 0.709 |
| | N (%) | N (%) | |
| Gender (counts) ^a | | | |
| Female | 91 (76%) | 84 (70%) | 0.309 ^a |
| Male | 29 (24%) | 36 (30%) | |
| | Mean (SD) | Mean (SD) | |
| Duration of surgery (min) | 104 (24) | 101 (23) | 0.384 |
| Tourniquet time (min) | 82 (33) | 81 (34) | 0.595 |
| Blood loss (mL) | 160 (135) | 201 (160) | 0.065 |
| Total crystalloid (mL) | 2320 (625) | 2471 (697) | 0.123 |

There were no significant differences between the treatment groups.

^a χ^2 test.

intent-to-treat analysis for the secondary end points of the study. An intent-to-treat analysis for the primary outcome (at 6 mo) was performed on 113 and 115 patients, respectively, for the pregabalin and placebo groups. In the pregabalin and placebo groups, 7 and 5 patients, respectively, were lost to follow-up (Fig. 1).

Nine patients in the pregabalin group and 2 patients in the placebo group did not receive any postoperative study medication. These 11 patients were included in the intent-to-treat analysis for both the primary and secondary end points, where there were data, because a single preoperative dose alone may influence postoperative outcomes. The reasons why the 9 patients in the pregabalin group did not receive any postoperative medication included 4 patients who withdrew consent after the operative procedure (1 secondary to sedation), 3 surgical cancellations (for reasons unrelated to the study protocol), 1 postoperative arrhythmia, and 1 unsuccessful spinal-epidural placement. The reasons for withdrawal in the control group included 1 unsuccessful spinal-epidural placement and 1 patient with severe early postoperative hypotension. Another 4 patients in the pregabalin group and 1 patient in the placebo group received <14 days of postoperative study medication and were also included in the intent-to-treat analysis. Demographic characteristics and intraoperative variables were similar between the 2 treatment groups (Table 1).

Adverse Events

Sedation, confusion, and dry mouth occurred more frequently in the pregabalin group than in the placebo group on the day of surgery and the first postoperative day (Table 2). By postoperative day 2, no adverse event reached statistical significance. There were no falls in this studied population that the investigators observed. No extra physician consults were needed for adverse effects such as sedation. If sedation occurred, we compensated by reducing the basal epidural analgesic flow rate. At the 6-mo postoperative

patient visit, there were no clinically significant adverse events in either group.

Outcome Measures

Chronic Neuropathic Pain and Related Outcomes

The incidence of neuropathic pain at 3 and 6 mo postsurgery was less frequent in the pregabalin group compared with the placebo group. At 3 mo, the incidence of neuropathic pain after TKA was 0% (0 of 113 patients) in the pregabalin group compared with 8.7% (10 of 115) in the placebo group ($P = 0.001$). The incidence of allodynia in the operated leg was also lower ($P = 0.002$) at 3 mo for the pregabalin group (2%, 2 of 113) than for the placebo group (12%, 14 of 115); the incidence of hyperalgesia in the operated leg was lower ($P = 0.009$) at 3 mo for the pregabalin group (8%, 8 of 113) than for the placebo group (20%, 23 of 115). At 6 mo postoperatively, the incidence of neuropathic pain was 0% (0 of 113) in the pregabalin group and 5.2% (6 of 115) in the placebo group ($P = 0.014$). The incidence of allodynia in the operated leg was also lower ($P = 0.002$) at 6 mo for the pregabalin group (0%, 0 of 113) than for the placebo group (8%, 9 of 115); the incidence of hyperalgesia in the operated leg was lower ($P = 0.006$) at 6 mo for the pregabalin group (2%, 2 of 113) than for the placebo group (11%, 12 of 115). The neuropathic pain in all 6 patients with an S-LANSS score of 12 or more at 6 mo was confirmed by physical examination by the physician. All 6 patients had allodynia and hyperalgesia to touch, and 5 of 6 had abnormal response to pinprick. There was no difference in preoperative pain scores ($P = 0.343$) between the pregabalin group (NRS = 7.7 ± 1.9 , $n = 67$) and the placebo group (NRS = 8.0 ± 1.3 , $n = 66$). As for concomitant analgesic use, 32 of 240 patients used NSAIDs during this 6-mo postoperative period, 16 in the pregabalin group and 16 in the placebo group ($P = 1.000$). Twenty-four of 240 patients used opioids during this postoperative period, 15 in the pregabalin group and 9 in the placebo group ($P = 0.282$). Eight of 240 patients used gabapentin or pregabalin during this postoperative period, 0 in the pregabalin group and 8 in the placebo group ($P = 0.007$). Twenty-four of 240 patients used acetaminophen/tramadol during this postoperative period, 11 in the pregabalin group and 13 in the placebo group ($P = 0.830$).

The KOOS-PS knee function score (0–100) for patients with chronic pain at 6 mo (all 6 in placebo group) was increased, 49.0 ± 16.2 , compared with 6 age-matched pregabalin patients, 12.4 ± 5.5 ($P = 0.003$), and also compared with 6 age-matched placebo nonchronic pain patients, 25.7 ± 7.2 ($P = 0.012$).

Range of Motion

Patients in the pregabalin group had greater active flexion of the operated knee during postoperative days 1–30 compared with placebo patients (mixed model: fixed effect, $F = 6.23$, $P = 0.013$), and change over time was highly significant ($P < 0.0001$) (Fig. 2).

Table 2. Incidence of Adverse Events on Day of Surgery (Day 0), Postoperative Days 1 and 2

| | Day 0 | | Day 1 | | Day 2 | |
|------------------|------------------------------|---------------------------|------------------------------|---------------------------|------------------------------|---------------------------|
| | Pregabalin <i>n</i> = 120 | Placebo <i>n</i> = 120 | Pregabalin <i>n</i> = 106 | Placebo <i>n</i> = 110 | Pregabalin <i>n</i> = 100 | Placebo <i>n</i> = 106 |
| Sedation | 16 (13%) | 4 (3%) | 28 (26%) | 15 (14%) | 15 (15%) | 8 (8%) |
| <i>P</i> | | 0.005* | | 0.019* | | 0.0906 |
| Confusion | 6 (5%) | 0 (0%) | 14 (13%) | 4 (4%) | 9 (9%) | 4 (4%) |
| <i>P</i> | | 0.013* | | 0.011* | | 0.123 |
| Dizziness | 1 (1%) | 1 (1%) | 18 (17%) | 12 (11%) | 10 (10%) | 8 (8%) |
| <i>P</i> | | 1.00 | | 0.197 | | 0.533 |
| Headache | 1 (1%) | 0 (0%) | 3 (3%) | 0 (0%) | 1 (1%) | 0 (0%) |
| <i>P</i> | | 0.316 | | 0.076 | | 0.302 |
| Dry mouth | 3 (3%) | 0 (0%) | 7 (7%) | 1 (1%) | 5 (5%) | 3 (3%) |
| <i>P</i> | | 0.081 | | 0.027* | | 0.421 |
| Nausea | 9 (8%) | 10 (8%) | 13 (12%) | 16 (15%) | 6 (6%) | 8 (8%) |
| <i>P</i> | | 0.811 | | 0.642 | | 0.659 |
| Vomiting | 3 (3%) | 3 (3%) | 4 (4%) | 6 (6%) | 1 (1%) | 3 (3%) |
| <i>P</i> | | 1.00 | | 0.479 | | 0.341 |
| Pruritus | 1 (1%) | 6 (5%) | 4 (4%) | 8 (7%) | 1 (1%) | 3 (3%) |
| <i>P</i> | | 0.055 | | 0.262 | | 0.341 |
| Peripheral edema | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) |
| <i>P</i> | | 1.00 | | 0.316 | | 1.00 |
| Diplopia | 1 (1%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| <i>P</i> | | 0.316 | | 0.323 | | 1.00 |

* There was a statistically significant difference ($P < 0.05$) between groups.

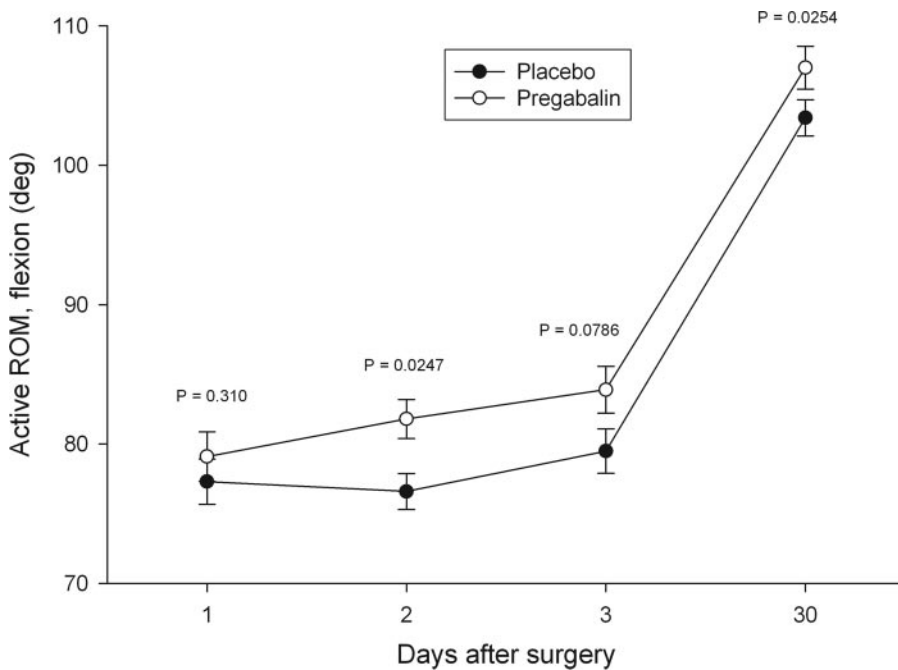


Figure 2. Active range of motion (ROM) of operated knee over postoperative days 1–30 showing greater flexion in the pregabalin group. Data plotted as mean ± SE.

Passive ROM during postoperative days 1–3 was also improved in the pregabalin group compared with the placebo group (mixed model: fixed effect, $F = 4.41$, $P = 0.037$), and change over time was highly significant ($P = 0.0013$). Passive ROM on Day 2 was $88.9^\circ \pm 9.9^\circ$ in pregabalin patients compared with $83.7^\circ \pm 15.2^\circ$ in placebo patients ($P = 0.012$).

Epidural Drug Use and Pain Assessment

In the immediate postoperative period, epidural drug consumption was less in the pregabalin group (5.77 ± 1.31 mL/h) than in the placebo group (6.40 ± 1.26 mL/h;

$P = 0.003$). In addition, the number of epidural PCEA boluses delivered was less in the pregabalin group (0.36/h [0.21–0.55], median [interquartile range]) than in the placebo group (0.63/h [0.30–0.98]) ($P = 0.009$). However, the frequency of a PCEA bolus is a difficult assessment of pain because a patient taking pregabalin who is sedated will likely not push the button for a bolus. In accordance with the study protocol, the NRS values at rest, during the immediate postoperative phase, did not differ between treatment groups (mixed model: fixed effect, $F = 2.77$, $P = 0.098$; and no change

over time [$F = 2.14, P = 0.0750$]). This is consistent with the instruction given to the study patients to maintain their pain score between 2 and 4 using PCEA bolus doses. However, the NRS values tended to be lower with pregabalin than with placebo at the discharge physical therapy session, during both active ROM (5.2 ± 2.4 vs $6.1 \pm 2.4; P = 0.059$) and passive ROM (6.0 ± 2.3 vs $7.0 \pm 2.2; P = 0.032$) testing. Supplemental postoperative oral opioid use (in morphine equivalents) to control pain over the entire hospital stay was less in the pregabalin group, 4.55 mg (2.40–9.16), compared with the placebo group, 7.32 mg (4.32–10.70) ($P = 0.005$). The dosage of metoclopramide and ondansetron used postoperatively by the patients with neuropathic pain at 6 mo (all in the placebo group) versus those without pain (all remaining patients combined) did not differ for either metoclopramide ($P = 0.8099$) or ondansetron ($P = 0.4374$).

Time to Meeting Hospital Discharge Criteria

Patients who were in the pregabalin group met hospital discharge criteria faster than patients in the control group (mean 60.2 ± 15.8 h compared with 69.0 ± 16.0 h, respectively; $P = 0.001$). The actual hospital discharge time, however, was not different between the 2 groups (mean time to discharge with pregabalin was 72.1 ± 18.8 h compared with 73.2 ± 15.6 h with placebo; $P = 0.702$).

Sleep Disturbance

The pregabalin patients had less sleep interference compared with placebo patients (mixed model: fixed effect, $F = 4.50, P = 0.038$), and change over time was highly significant ($P < 0.0001$) while in the hospital. On the first postoperative night, the sleep interference score was 2.9 ± 3.3 for the pregabalin group compared with 4.6 ± 3.2 for the placebo group (stepdown Bonferroni: $P = 0.035$). On each succeeding night, there were no statistical differences between groups.

DISCUSSION

The principal finding from this randomized, placebo-controlled trial of perioperative administration of pregabalin to patients undergoing TKA was a significant decrease in the incidence of chronic neuropathic pain (0% compared with 5.2% in the placebo group) at 6 mo after surgery. The reported incidence of chronic neuropathic pain after TKA has varied between 0.8%²⁰ and 12.7%⁴ at 6 mo postoperatively. In a recent report on a small number of patients ($n = 20$) undergoing TKA, none of the patients had tactile allodynia, or decreased mechanical or thermal pain thresholds (signs and symptoms of neuropathic pain), but 20% of the patients had moderate chronic pain at 4 mo postoperatively.²¹ The wide variation in prevalence estimates is likely related to retrospective study designs, variable criteria for neuropathic pain, or small sample size.⁴ Neuropathic pain of the operated knee can result in substantial discomfort and limit

activities of daily living. This is the first large prospective clinical trial examining the incidence of chronic neuropathic pain after TKA and defining a strategy to prevent the development of this distressing chronic pain syndrome.

In a similar study, the administration of gabapentin to women undergoing total abdominal hysterectomy did not reduce acute postoperative pain, but there was a decrease in pain at 1 mo postoperatively.²² A preoperative dose of 1200 mg was chosen for that study, and it was repeated daily for the first 7 days postoperatively. In another study of abdominal hysterectomy, gabapentin was given at 1800 mg/day starting 1 h preoperatively for 72 h, but long-term pain was not evaluated.²³ Similarly, we designed our study with the intent to prevent spinal cord sensitization by preoperatively administering a recommended upper limit dose (300 mg) of pregabalin that was continued for 14 days after surgery (150 mg twice daily for 10 days and then titrated down for another 4 days). Although we chose a 14-day postoperative regimen, the minimum duration or the dose required to prevent the long-term sequelae of spinal cord sensitization after a major surgery such as TKA cannot be determined from this study.

Chronic neuropathic pain is a complex condition that has a profound effect on both quality of life and expenditures for health care.²⁴ This was evident by the results of our study, demonstrating reduced knee function (higher level of KOOS-PS scores) at 6 mo postoperatively in patients with neuropathic pain (in the placebo group of patients) compared with patients without chronic pain. Treatment options for patients who develop neuropathic pain after TKA are challenging and expensive. Patients who undergo repeated TKA for chronic pain of the knee invariably have further exacerbation in knee pain, and in very rare instances, above-knee amputations have been reported.²⁵

In a large study of 10,000 patients with osteoarthritis who underwent TKA, a 2-yr postsurgery survey showed that patients who had persistent pain in the knee had decreased functional improvements.²⁶ Oral perioperative administration of pregabalin improved active and passive ROM after TKA in our study. ROM is an important measure of outcome after TKA.²⁷ It has been demonstrated that 67° of knee flexion is needed for the swing phase of gait, 83° to climb stairs, 90° to descend stairs, and 93° to rise from a chair after TKA.²⁸ Higher degrees of ROM to 106° are required for activities such as shoe tying.²⁹ The active knee flexion (79.5°) attained in our placebo group by Day 3 (typical discharge day) is similar to that reported in other studies using postoperative regional analgesia after TKA.^{30,31} The pregabalin group, however, demonstrated greater knee functionality (83.9° active flexion = stair climbing) at discharge. It is likely that this beneficial effect on knee function at time of discharge facilitated attainment of nearly full functionality in the pregabalin group (107.0° active flexion = shoe tying)

at 1 mo after surgery, versus 103.4° in the placebo group. These beneficial effects have important economic implications for reducing the costs associated with the additional time in physical therapy necessary to achieve full knee function.³²

The beneficial outcomes associated with pregabalin in this study may be related to presurgical administration of a large initial dose and/or a continued large dose for 10 days after TKA. Our first dose at 1–2 h before surgery was not intended to be “preemptive analgesia.” Instead, it was to provide coverage immediately after surgery, when it would have been difficult to administer this oral medication. A recent study with the cyclooxygenase-2 inhibitor celecoxib failed to find a benefit to perioperative administration compared with postoperative administration alone.³³ Further studies are needed to assess the benefit, if any, of preoperative administration of pregabalin given the recent studies questioning its analgesic benefit in the early postoperative period and well-documented side effects.^{11–13,34} It has been suggested that aggressive management of early postoperative pain may reduce the likelihood of long-term pain,³⁵ and this concept has been extended to other surgical procedures that are followed by persistent pain.³ Because our protocol was designed to actively manage acute postoperative pain equally in both the pregabalin and the placebo groups, the reduction in the incidence of long-term postoperative pain after TKA cannot be attributed to amelioration of acute pain. Nevertheless, the ability of pregabalin to reduce short-term central nervous system hypersensitivity in humans³⁶ makes it likely that early and maintained reduction of neuronal excitability by this drug is one possible mechanism for suppression of long-term neuropathic pain. The mechanism of action of pregabalin probably involves binding to voltage-gated calcium channels,³⁷ which are upregulated in the dorsal root ganglia and spinal cord in rat neuropathic pain models.³⁸ The reduction in sleep interference in the pregabalin group may be, in part, attributable to the increased sedation also seen in that group.

There were no statistically significant differences in the actual recorded duration of hospitalization between the 2 groups. With newer treatment strategies for TKA patients, multidisciplinary operational changes are needed to facilitate an earlier discharge from the hospital.³⁹

The 300-mg initial pregabalin dose (before surgery), without the slow dose escalation that is standard practice when pregabalin (or gabapentin) is administered for chronic pain, most likely led to the increased incidence of sedation and confusion in the pregabalin-treated patients during the immediate postoperative period. In a study of pregabalin 100 mg given before minor gynecological surgery, the incidence of lightheadedness, visual disturbance, and difficulty with walking was more frequent with pregabalin than with placebo at 24 h after surgery.¹¹ The 300-mg dose of

pregabalin given before surgery produced higher sedation scores at 90 and 120 min after elective ambulatory and short-stay surgery compared with placebo.¹² When given to reduce shoulder pain after laparoscopic cholecystectomy, 150 mg of pregabalin given presurgery produced oversedation at the 2-h time point after surgery compared with placebo.¹³ Therefore, lower pregabalin doses should be considered in future studies to minimize such side effects, and hopefully, maintaining therapeutic efficacy. One of the limitations of this study is the absence of dose-response data. Our initial intent with this study was to establish whether administering pregabalin at this selected high dose was effective in preventing chronic pain. Furthermore, large clinical studies with lower doses and shorter duration are necessary to determine the optimal dose and duration of intervention required to achieve similar results in this and other surgical pain models. Although the S-LANSS neuropathic pain ratings are a validated assessment tool,¹⁶ a full clinical examination of all patients enrolled in the study is always preferred. There was no difference in use of NSAIDs, opioids, or acetaminophen/tramadol between the pregabalin and placebo groups in the 6-mo postsurgery period. Placebo group patients were prescribed more gabapentin or pregabalin during this postoperative period than the pregabalin group. Interpretation of this for placebo patients is inconclusive without additional timeline and prescribing information, but does support the fact that the pregabalin group effect was the result of treatment dosing. Although ondansetron has been shown to produce modest transient analgesia in patients with neuropathic pain,⁴⁰ the use of this drug was not increased in patients who did not develop neuropathic pain. Finally, because all of our patients had epidural analgesia, the results of this study may not apply to patients receiving perioperative IV or oral analgesics for TKA.

In summary, this study validates the efficacy of the perioperative use of pregabalin to reduce chronic neuropathic pain after TKA. In addition, pregabalin also shortens the time to achieve effective joint ROM.

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Hemispheric Synchronized Sounds and Perioperative Analgesic Requirements

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BACKGROUND: Data on the effect of Hemisync® sounds on perioperative analgesic requirements are scant.

METHODS: We randomized surgical outpatients into a treatment group that received Hemisync sounds ($n = 20$), a music group that received music ($n = 20$), and a control group that had a blank cassette tape ($n = 20$). All subjects underwent a controlled standardized propofol-nitrous-vecuronium and fentanyl general anesthesia.

RESULTS: The treatment group had significantly reduced intraoperative fentanyl consumption ($P < 0.05$). Postoperatively, pain visual analog scale scores were significantly lower in the Hemisync group at 1 h ($P = 0.02$) and 24 h ($P = 0.005$). Subjects in the Hemisync group were also discharged earlier ($P = 0.048$).

CONCLUSION: The use of Hemisync sounds before and during general anesthesia reduces intraoperative analgesic requirements, postoperative pain scores, and discharge time.

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Two auditory impulses with a difference in frequency between 1 and 30 Hz, when presented simultaneously to both ears, can result in a perception of the difference between the 2 tones as a single auditory binaural beat.¹⁻³ Such binaural beats have been described to be brainstem responses that originate in the superior olivary nucleus of each cerebral hemisphere and are thought to cause hemispheric synchronization.^{1,2} This modality is promoted as a treatment for stress, anxiety, pain control, and other conditions (<http://www.monroeinstitute.org>). Kliempt et al.³ reported that subjects who were exposed to Hemisync® sounds under general anesthesia consumed significantly less intraoperative fentanyl. Lewis et al.⁴ confirmed these findings in a group of patients undergoing bariatric surgery who were treated with Hemisync sounds. In contrast, Dabu-Bondoc et al.⁵ found that Hemisync sounds do not reduce the hypnotic component of an anesthetic state in a group of patients undergoing outpatient surgery. None of these previous studies, however, examined the effects of Hemisync sounds on postoperative pain and analgesic requirements. As

such, we designed the following randomized controlled study to also examine the effect of Hemisync on postoperative pain and analgesic requirements.

METHODS

Subjects included outpatients aged 18–65 years, ASA physical status I–II, undergoing outpatient surgery requiring general anesthesia. IRB approval was obtained and each patient consented. Subjects with a history of consuming psychiatric medications or hearing impairment were excluded. On the day of surgery, demographic data and trait anxiety (State Trait Anxiety Index) were obtained from each participant. The State Trait Anxiety Index is a widely used and well-validated self-report anxiety assessment instrument.⁶

Subjects were randomized into 3 groups, and all subjects were given headsets. The treatment group received Hemisync tapes marketed as “surgical support,” the music group received a music tape of their choice, and the control (placebo) group received a blank cassette tape that produced white noise when played. In the preoperative holding area, all subjects received the designated intervention for 30 min via a headset. None of the subjects was offered any sedative premedication. The anesthesiologist and the postanesthesia care unit (PACU) caregiver were blinded to group assignment of each patient. A blank cassette tape was used for the control group, and all tapes looked similar. Headsets from all groups of participants were removed before the patients entered the operating room and restarted after the induction of anesthesia for all participants. Headsets were discontinued at the conclusion of surgery, patients were

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Table 1. Baseline Characteristics

| | Hemisync® group | Music group | Control group | P |
|------------------------------------|-----------------|-------------|---------------|-------|
| Age (yr) | 42 ± 14 | 41 ± 13 | 41 ± 10 | 0.94 |
| Education (yr) | 15.5 ± 3 | 13.9 ± 3 | 14.9 ± 3 | 0.19 |
| Sex (% male; % female) | 38/62 | 45/55 | 28/72 | 0.55 |
| State anxiety (STAI ^a) | 40 ± 13 | 42 ± 12 | 43 ± 11 | 0.65 |
| Trait anxiety (STAI ^a) | 35 ± 9 | 41 ± 11 | 40 ± 8 | 0.13 |
| Prior surgery (%) | 25/75 | 24/76 | 39/61 | 0.53 |
| Weight (kg) | 75 ± 15 | 77 ± 18 | 74 ± 18 | 0.88 |
| Laparoscopic procedures | 10 | 11 | 11 | (54%) |
| Breast surgeries | 4 | 3 | 3 | (17%) |
| Orthopedic procedures | 4 | 4 | 3 | (19%) |
| Plastic surgeries | 2 | 2 | 2 | (10%) |

Continuous data were analyzed by one-way analysis of variance (ANOVA); categorical data were analyzed by χ^2 test.

Laparoscopic procedures included gynecologic and general laparoscopies; breast surgeries included lumpectomies and simple mastectomies; orthopedic procedures included repairs of fractures or tendons and arthroscopies; plastic surgeries included mammoplasties and abdominoplasties.

^a STAI = State Trait Anxiety Index.

allowed to recover in the PACU, and data collection was continued.

In the operating room, anesthetic technique was standardized for all patients, and a bispectral index (BIS) monitor (Aspect Medical Systems, Natick, MA) was applied on all patients. General anesthesia was induced with propofol (1 mg/kg), followed by a single dose of fentanyl (1 μ g/kg). After observing clinical responses and allowing for BIS equilibration (60 s), additional incremental doses of propofol (20–30 mg) were given to reach a BIS value of 40–60. Vecuronium (0.1 mg/kg) was given as required to facilitate endotracheal intubation. A laryngeal mask airway was used for procedures not requiring endotracheal intubation. Anesthesia was maintained with oxygen/nitrous oxide (1:2 L/min), and a propofol infusion 100–200 μ g/min, adjusted to maintain BIS in the 40–60 range. A heart rate and/or arterial blood pressure beyond 20% of baseline were treated with fentanyl in 25- μ g increments. To control for the confounding effects of various types of surgeries and different surgeons, patients were matched to control for specific surgical procedure and surgeon. In the PACU, patients were given no fentanyl when the visual analog scale (VAS) score was 0–3, 25 μ g of fentanyl for a VAS score of 4–6, and 50 μ g of fentanyl for a VAS score of 7–10. If patients required >200 μ g of fentanyl, analgesia was then supplemented with morphine in increments of 1–2 mg until the pain score reduced to 0–3. Amount of analgesics used, incidence of nausea/vomiting, oxygen desaturation, and pain (VAS) scores on arrival and every 10–20 min thereafter were measured in the PACU and then 24 h postoperatively. An independent observer who was blinded to group assignment collected data in the PACU. Subjects were all prescribed Percocet for pain after discharge. Subjects were followed up via a phone call 24 h after surgery.

The primary end point of this study was perioperative analgesic consumption. A sample size of 20 subjects in each group (yielding a total number of 60) provided 80% power to detect an effect size difference in consumption of 0.4 among groups, with an α of

0.05. The secondary end points included postoperative measurement of pain (VAS) scores. All analgesics consumed (morphine, fentanyl, and Percocet) were converted to IV morphine milligram equivalents. Comparisons among groups were analyzed with χ^2 test for categorical data and 1-way analysis of variance for continuous data. Data are presented as mean \pm SD. $P < 0.05$ was considered significant. Analysis was conducted using SPSS statistical software (SPSS, Chicago, IL).

RESULTS

Demographic and personality characteristics did not differ among the 3 groups and are presented in Table 1. Similarly, perioperative propofol consumption adjusted for weight and length of procedure did not differ among the 3 groups (Table 2). Analysis showed that the Hemisync group required significantly less fentanyl during the anesthetic procedure compared with the music or control group (Table 2, $P = 0.046$). *Post hoc* analysis showed that the difference was significantly lower between the Hemisync and the music group ($P = 0.024$) and between the Hemisync and the control group ($P = 0.045$).

Analgesic consumption was similar among the 3 groups both in the PACU and during the first 24 h postoperatively ($P =$ not significant). Pain VAS scores at 1 h in the PACU and at 24 h after surgery were significantly lower in the treatment group compared with the music and control groups ($P = 0.02$ and $P = 0.005$, respectively). Discharge time from the PACU was also lesser in the Hemisync group compared with the other 2 groups ($P = 0.048$). The 3 groups were similar in terms of incidence of nausea and vomiting, oxygen desaturation, recall, and patient satisfaction. Finally, intraoperative average heart rate and arterial blood pressure did not differ significantly among the 3 groups ($P =$ not significant).

DISCUSSION

Consistent with previous studies,^{3,4} our study demonstrates that listening to Hemisync sounds results in

Table 2. Perioperative Outcome Data

| | Variable Hemisync® group | Music group | Control group | P |
|--|--------------------------|--------------|---------------|-------|
| Intraoperative fentanyl ^a | 14.6 ± 6.9 | 20.9 ± 9.1 | 20.3 ± 9.4 | 0.046 |
| Postoperative (PACU) analgesic ^b | 15.0 ± 12.9 | 14.4 ± 13.2 | 16.9 ± 12.8 | 0.83 |
| Postoperative (home) analgesic ^b | 18.6 ± 11.6 | 28.0 ± 16.4 | 25.0 ± 13.1 | 0.099 |
| Total perioperative analgesic | 48.3 ± 21.8 | 62.6 ± 29.1 | 61.7 ± 24.0 | 0.14 |
| VAS score T0 in PACU | 3.8 ± 3.4 | 4.5 ± 3.3 | 5.4 ± 2.5 | 0.30 |
| VAS score T10 in PACU | 4.0 ± 3.3 | 3.8 ± 2.7 | 5.2 ± 2.3 | 0.26 |
| VAS score T20 in PACU | 3.6 ± 2.8 | 4.5 ± 2.4 | 4.3 ± 2.2 | 0.52 |
| VAS score T30 in PACU | 3.5 ± 2.0 | 3.4 ± 1.4 | 4.1 ± 2.4 | 0.54 |
| VAS score T60 in PACU | 2.6 ± 1.6 | 4.2 ± 2.1 | 3.9 ± 1.7 | 0.02 |
| VAS score 24 h postoperatively | 3.5 ± 1.5 | 5.3 ± 1.8 | 5.0 ± 2.0 | 0.005 |
| Discharge time | 120.2 ± 37.3 | 156.6 ± 65.6 | 162.8 ± 68.2 | 0.048 |
| PONV | 0.1 ± 0.5 | 0.2 ± 0.4 | 0.2 ± 0.4 | 0.61 |
| Recall | 0 | 0 | 0 | NA |
| Patient satisfaction | 3.9 ± 0.2 | 4.0 ± 0.2 | 3.9 ± 0.4 | 0.12 |
| Total propofol infusion time (min) | 82.6 ± 23.8 | 105.6 ± 44.2 | 108.0 ± 58.9 | 0.15 |
| Total propofol ($\mu\text{g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) ^c | 0.18 ± 0.06 | 0.17 ± 0.04 | 0.20 ± 0.13 | 0.43 |
| Systolic blood pressure | 113.2 ± 14.5 | 112.6 ± 11.9 | 116.5 ± 10.4 | 0.58 |
| Diastolic blood pressure | 68.8 ± 9.5 | 66.3 ± 9.7 | 72.3 ± 11.8 | 0.21 |
| Heart rate | 71.3 ± 6.4 | 69.9 ± 7.9 | 72.4 ± 9.4 | 0.63 |

PACU = postoperative care unit; VAS = visual analog scale; PONV = postoperative nausea and vomiting; NA = not applicable.

^a Fentanyl requirements in microgram converted to IV morphine equivalents in milligram.

^b Analgesic requirements in total IV morphine equivalents in milligram.

^c Total propofol dose and infusion time include both induction and maintenance.

decreased use of intraoperative analgesics in surgical patients who undergo general anesthesia. This study, however, differed from previous studies^{3–5} because it also explored postoperative analgesic requirements, and we provided Hemisync music both before and during general anesthesia. The reader should note that in previous studies, subjects listened to Hemisync sounds only while under general anesthesia. We found that although analgesic consumption in the PACU was similar among the 3 study groups, analgesic consumption after discharge from the PACU was about 30% lower in the Hemisync group compared with the control and music groups, respectively, but *post hoc* comparisons among groups did not show consistent statistical difference. The negative effect in analgesic consumption in the PACU may have been due to the following. First, approximately 25% of the subjects underwent relatively minor and short surgical procedures, such as hysteroscopy and tubal ligation, which generally required relatively minimal postoperative analgesia or even no analgesia at all. This could have potentially diluted the positive effect of the intervention. Second, this could be a case of a Type II statistical error. That is, a false negative effect secondary to a sample size that is not large enough. Although we have calculated an *a priori* sample size, this calculation may have been based on a better than expected effect size.

Pain (VAS) scores were significantly decreased at 1 h (T60) after arrival in the PACU and at 24 h after

discharge. These results were consistent with delay in manifestation of effect in analgesic consumption. The consistency of effect in 2 parameters seems to be strongly suggestive of the potential positive effect of listening to Hemisync on postoperative pain requirements. Why there was a delay in effect by the intervention also remains to be further investigated.

In conclusion, under the condition of this study, we found that listening to Hemisync sounds before and during surgery results in decreased consumption of intraoperative analgesics as well as lower postoperative pain scores and earlier discharge from the PACU. This consistency of effect in 2 parameters seems to be strongly suggestive of the potential positive effect of listening to Hemisync on postoperative pain requirements.

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The First Scintigraphic Detection of Tumor Necrosis Factor-Alpha in Patients with Complex Regional Pain Syndrome Type 1

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Tumor necrosis factor (TNF)- α has been identified as a pathogenic factor in many immunologically based diseases and complex regional pain syndrome (CRPS). In this case series, we used radiolabeled technetium anti-TNF- α antibody to scintigraphically image TNF- α in 3 patients with type 1 CRPS. The results show that TNF- α was localized only in affected hands of patients with early-stage CRPS. No uptake was seen in clinically unaffected hands and late-stage CRPS. Our findings support the growing evidence for neuroimmune disturbance in patients with CRPS and may have important further implications for specific anticytokine treatment in patients with CRPS.

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Complex regional pain syndrome (CRPS) is a well-described complication after trauma or operation with a prevalence of about 30 per 100,000.¹ It is characterized by spontaneous pain that is often accompanied by somatosensory disturbances such as mechanical hyperalgesia and thermal or mechanical hyperalgesia. Other clinical signs include edema, disturbed blood flow of the skin, and abnormal sudomotor activity in the affected limb. CRPS is a clinical diagnosis and should be differentiated from ordinary posttraumatic or postoperative findings and by exclusion of other conditions or diseases.¹⁻³ CRPS has a relevant social impact because it frequently causes severe longstanding disability in afflicted patients.⁴

To date, no imaging studies to detect tumor necrosis factor (TNF)- α *in situ* have been performed in patients with CRPS. The main objective of this pilot case series was to detect TNF- α *in situ* in the affected

limbs of 3 patients with CRPS by performing technetium 99m (^{99m}Tc)-anti-TNF- α antibody (influximab) scintigraphy (TNFaS).

CASE DESCRIPTION

All procedures of this case series were performed in accordance with German national and local ethics committee rules of the Hannover Medical School, and all patients had to sign an informed consent.

We identified 3 patients referred consecutively to the Pain Clinic at the Hannover Medical School as CRPS type 1 patients suitable for enrollment in the case series based on the diagnostic criteria of the 1993 Consensus Conference of the International Association for the Study of Pain and the advanced research criteria later published by Bruehl et al.^{2,5}

Skin temperature was assessed using an infrared temperature-measuring device (RayTec, Schlender, Berlin, Germany). Measurements were obtained on the dorsal aspect of the hands and compared among affected and unaffected sides.

After an IV bolus injection of 580–620 MBq (7 MBq/kg; body weight adjusted) ^{99m}Tc-methylene diphosphonate, bilateral image sequences were recorded for 0–120 s (angiographic Phase 1) for each patient. A static image (100 s) and a whole body scan (speed: 30 cm/min) followed consecutively (blood pool Phase 2). More than 2 h later, a whole body scan (speed: 12 cm/min) and special regional images (3 min each) were performed to assess bone mineralization (Phase 3).

After clinical and scintigraphic substantiation of CRPS type 1 diagnosis, a small dose (500 μ g) of 550 MBq ^{99m}Tc-labeled anti-TNF- α antibody influximab (Remicade®, Centocor B.V., Leiden, The Netherlands) was administered (IV) with subsequent sequential scintigraphy of the affected region and whole body. The aim was to evaluate *in vivo* distribution of the anti-TNF- α antibody and identify and detect a specific accumulation of TNF- α *in situ* in the

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Table 1. Demographic Data and Clinical Aspects

| Patient | CRPS 1 "Warm Type" | Age (yr) | Gender (male/female) | Onset of symptoms (mo) | Temperature difference (°C) |
|---------|-----------------------|-------------|-------------------------|---------------------------|--------------------------------|
| 1 | Right hand | 58 | Female | <3 (early stage) | +2.0 |
| 2 | Left hand | 37 | Male | <3 (early stage) | +2.1 |
| 3 | Right hand | 22 | Female | >24 (late stage) | +0.3 |

CRPS = complex regional pain syndrome.

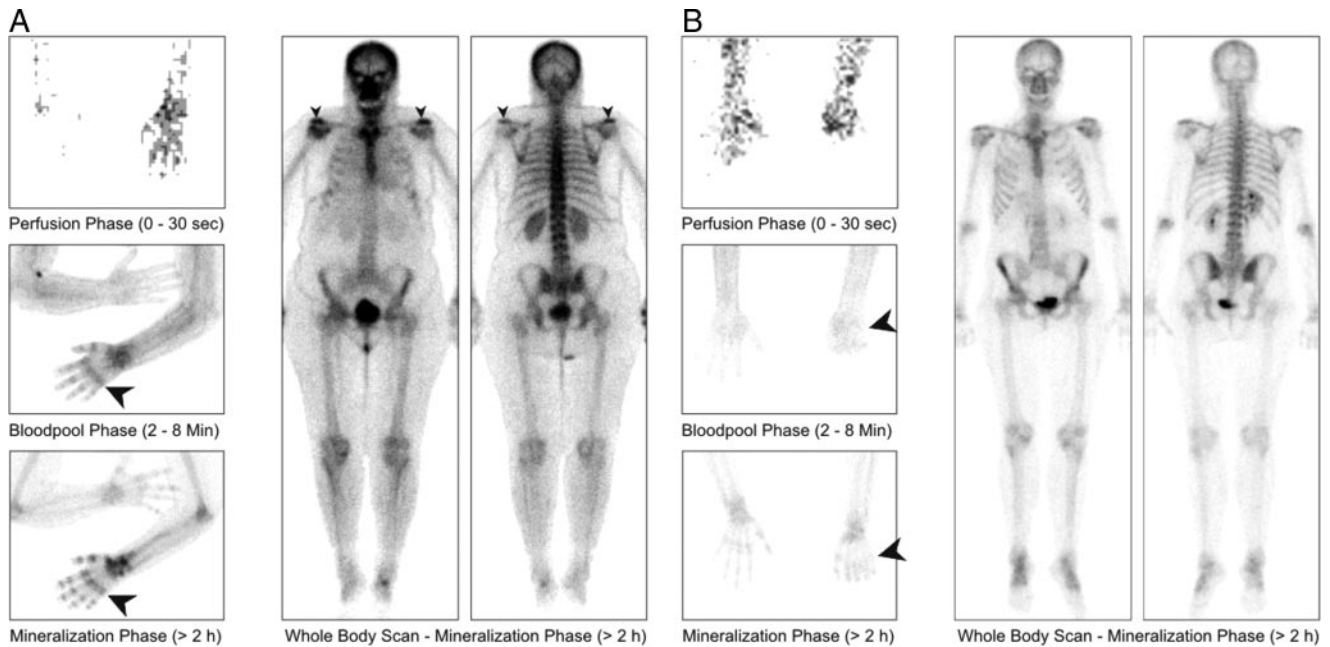


Figure 1. A, Three-phase bone scintigraphy (TPBS) of Patient 1 (Table 1, early-stage complex regional pain syndrome [CRPS]). Blood pool images indicate hyperemia within the right wrist and metacarpophalangeal (MCP) joints 1–5 (affected side, large arrowhead). Increased tracer accumulation also in the third phase around MCP joints, proximal interphalangeal (PIP) joints, and distal interphalangeal (DIP) joints. Note the increased enhancement in both shoulders (acromioclavicular joints, sternoclavicular joints, and glenohumeral joints) in terms of osteoarthritis (small arrowheads). B, TPBS of Patient 3 (Table 1, late-stage CRPS). No increased tracer uptake could be detected in the affected hand.

CRPS-affected regions of the body. The approved anti-TNF- α antibody infliximab (Remicade) was labeled with ^{99m}Tc using slightly modified methods from those reported by Blankenberg et al.⁶ and Barrera et al.⁷

Whole body and regional images of the affected upper extremity of each patient were obtained using a double-headed γ camera (DIACAM, syngo workstation, Siemens, Germany) at 5 min, 1 h, 4 h, and 21 h after injection. Activity accumulation at the affected joints was measured and compared, after background correction, with that at the corresponding contralateral, unaffected joints.

All examined patients ($n = 3$) had CRPS type 1 of the hand ("warm type"; forearm not usually involved) after distal radial fracture (Table 1), assuring a homogeneous picture of the disease. Two patients had early-stage CRPS and 1 patient late-stage CRPS, but a substantial temperature difference was only observed between affected and unaffected sides in the early stage (Table 1). Patients underwent 3-phase bone scintigraphy and TNFaS after a 1-wk time interval. The procedures were well tolerated, and side effects/adverse events did not occur.

The 3-phase bone scintigraphy (Fig. 1A) presented the characteristic picture of an early-stage CRPS of the right hand (e.g., Patient 1, Table 1; similar image also found in Patient 2). Blood pool images indicated hyperemia within the right (affected) wrist and the metacarpophalangeal (MCP) joints 1–5. Significant uptake also occurred by the wrist and MCP joints 1–5 in the third phase (2 h) and in the

acromioclavicular and sternoclavicular joints, typically found in osteoarthritis of the shoulder joints (Fig. 1A, small arrowheads). No increased tracer uptake was detected in the affected hand of the late-stage patient (Fig. 1B).

Figure 2 shows the biodistribution of the ^{99m}Tc -anti-TNF- α antibody illustrated by the anterior whole body images of Patient 1. In both early-stage patients, the antibody was localized in CRPS-affected hands within minutes after injection. Wrist and MCP joints were even more clearly visualized 4 and 21 h after injection. Uptake of the antibody in inflamed joints (Fig. 2 and Table 2) was at least 2-fold that of the periarticular normal tissue of the unaffected contralateral side. Similar data were obtained for the other early-stage patient. The antibody was cleared from blood with a median biological half-life ($T_{1/2}$) of 44 h.

Antibody uptake was not observed in the unaffected hands of any patient, in the affected hand of the patient with late-stage CRPS (Fig. 3A), and, interestingly, not in the osteoarthritis-affected shoulder joints of Patient 1 (Fig. 2A, small arrowheads). Tracer activity in the unaffected MCP joints of the left hand decreased significantly after the initial peak (Fig. 2C). Obviously, there is no specific binding. In contrast, there was increasing tracer enrichment in the affected joints of the right hand during the total observation period (Fig. 2D). For this reason, hyperemia as a causative mechanism for the delayed activity concentration is unlikely. In the late-stage Patient 3 (Figs.

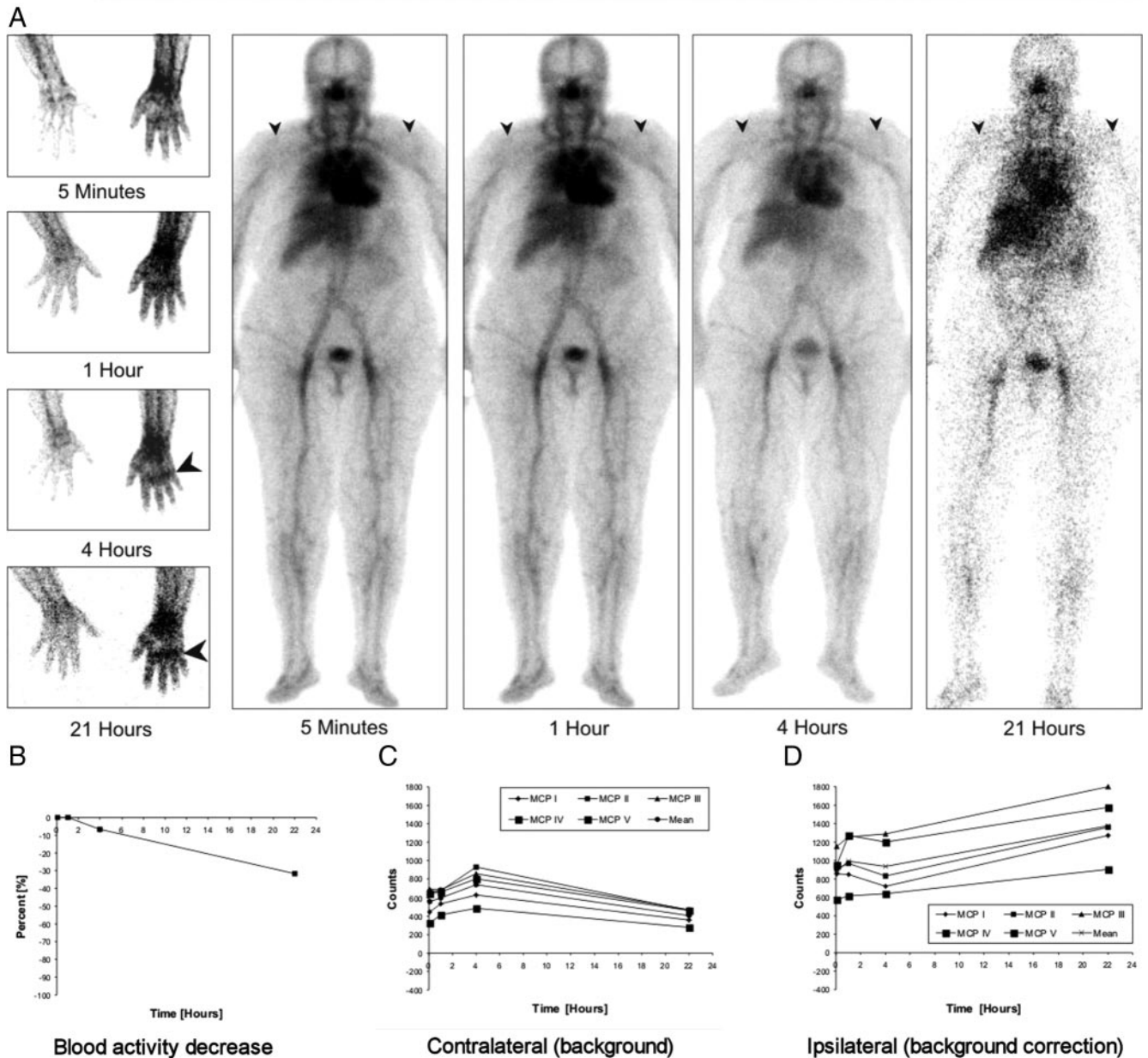


Figure 2. A, Technetium 99m -anti-tumor necrosis factor (TNF)- α antibody scintigraphy of Patient 1; B, declining blood pool activity curve (clearance); C, decreasing tracer concentration in the metacarpophalangeal (MCP) joints of the contralateral hand; D, increasing tracer concentration in the MCP joints of the affected hand.

Table 2. Percentage Change in 99m Tc-Anti-Tumor Necrosis Factor (TNF)-Alpha Antibody Uptake (4 vs >21 h p.i.) in MCP Joints

| MCP | Patient 1 | | Patient 2 | | Patient 3 | |
|------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|
| | Affected side (BC, %) | Unaffected side (%) | Affected side (BC, %) | Unaffected side (%) | Affected side (BC, %) | Unaffected side (%) |
| I | 76.7 | -43.0 | 18.3 | -38.0 | -69.7 | -40.1 |
| II | 63.5 | -50.6 | 45.3 | -38.7 | -247.1 | -26.3 |
| III | 39.9 | -45.4 | -8.8 | -13.3 | -7.5 | -37.6 |
| IV | 31.3 | -43.0 | 33.5 | -42.3 | -50.0 | -33.0 |
| V | 39.8 | -41.6 | 13.6 | -52.2 | -15.1 | -22.2 |
| Mean | 47.5 | -45.3 | 18.3 | -37.0 | -35.0 | -32.4 |

99m Tc = technetium 99m; BC = background correction; MCP = metacarpophalangeal.

3A–D), there was no specific tracer accumulation either in the affected or unaffected hand, and the activity decreased after the initial peak similar to the unaffected

hand (Figs. 3C and D). Taken together, Table 2 shows the percentage change in antibody uptake (4 vs >21 h after injection) for all patients.

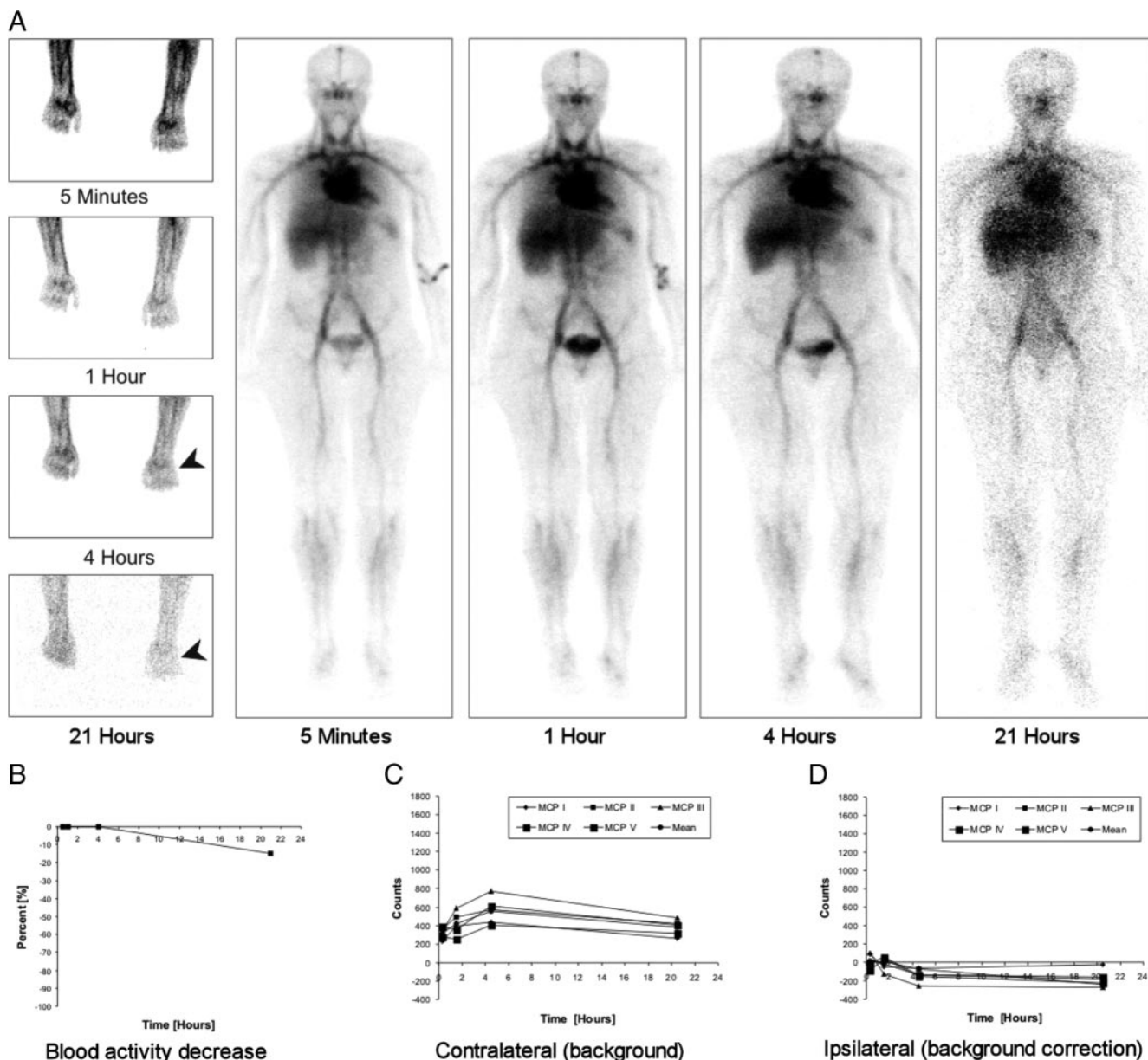


Figure 3. A, Technetium 99m-anti-tumor necrosis factor (TNF)- α antibody scintigraphy of Patient 3; B, declining blood pool activity curve; C, decreasing tracer concentration in the metacarpophalangeal (MCP) joints of the contralateral hand; D, no increasing tracer concentration in the MCP joints of the affected hand.

DISCUSSION

This is the first report to scintigraphically detect TNF- α *in situ* in patients with CRPS, showing specific tracer accumulation in early-stage CRPS type 1 but not in the late stage and in osteoarthritis-affected joints. The data add to the growing evidence of a neuroimmune disturbance in CRPS type 1.⁸⁻¹¹

However, since the first descriptions of the condition reported by Mitchell and Sudeck,¹² an inflammatory process has been suspected. Consequently, there is a continuing discussion about the role of proinflammatory cytokine profiles in CRPS and other neuropathic pain syndromes. Whereas some authors could not detect any abnormalities in interleukin (IL)-1, IL-6, IL-8, or IL-10 blood levels,¹³ others found increased

blood levels of IL-8 and soluble TNF- α receptor I and II.¹⁴ Maihofner et al.⁹ also found that soluble TNF- α receptor type I is significantly increased in type 1 CRPS, particularly if there is mechanical hyperalgesia. Moreover, in 1 study, proinflammatory blood cytokine mRNA and protein levels of the proinflammatory cytokines such as TNF- α , IL-2, and IL-8 were increased.¹⁰ On the basis of these findings, we performed the first successful IV regional block with administration of the TNF- α antibody infliximab for the treatment of CRPS type 1.¹⁵

TNF- α belongs to a family of proteins important in immune regulation and programmed cell death. It is expressed by many cells within the immune system and has a key role in inflammatory processes, including involvement in stimulating cytokines (including

its own) production, by enhancing the expression of adhesion molecules and by neutrophil activation.¹⁶

The recognition of the crucial roles of proinflammatory cytokines such as TNF- α , IL-1, or IL-6 in the inflammation process in rheumatoid arthritis (RA) has led to the development of targeted biological therapies, such as drugs that block the action of TNF- α . These biological treatments have revolutionized the treatment of RA and other rheumatic diseases, including ankylosing spondylitis, psoriasis arthritis, plaque psoriasis, and inflammatory bowel diseases.¹⁷

Barrera et al.⁷ reported the scintigraphic detection of TNF- α in patients with RA using a small dose of 100 μ g of the ^{99m}Tc-TNF monoclonal antibody adalimumab (Humira®, Abbot Laboratories, Chicago, IL). Adalimumab is approved, among other indications, for subcutaneous administration in the treatment of RA, and the radiolabeled anti-TNF monoclonal antibody allowed clear visualization of inflamed joints in patients with RA. We chose the antibody infliximab because Remicade is the only anti-TNF- α antibody approved for IV application.

In conclusion, the ^{99m}Tc-labeled anti-TNF- α antibody infliximab produced positive scintigraphic foci in early-stage type 1 CRPS but not in the late-stage patient and in osteoarthritis-affected joints. Our findings complement the recently published data of a neuroimmune disturbance and a local cytokine-induced inflammation in early-stage CRPS type 1.^{8–11} The use of labeled antibodies may offer the potential to stratify patients for targeted treatment options. Further methodical and controlled studies are needed.

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Transforaminal 5% Phenol Neurolysis for the Treatment of Intractable Cancer Pain

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This is the first case report of using a transforaminal approach for phenol administration. A 76-yr-old patient with a history of leiomyosarcoma and multiple metastatic lesions had unremitting pain in the right thoracic and lumbar regions and had prohibitive opioid-induced side effects. The patient underwent phenol neurolysis using a transforaminal approach in 2 stages at 3 levels (L3-4, L1-2, and T12-L1). The patient had complete resolution of pain, without any complications, and opioid treatment was nearly discontinued. Transforaminal phenol neurolysis is a reasonable treatment option for patients suffering from intractable pain for whom conventional therapies have proven ineffective.

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Advanced cancer is often associated with severe pain, and it has been estimated that 60%–90% of all patients dying of cancer will experience pain in the terminal phase of their disease.¹⁻³ Pain can be managed using nonsteroidal antiinflammatory drugs, opioids, and adjuvants following the World Health Organization analgesic guidelines.⁴ However, studies have shown that at least 10%–15% of patients will experience severe pain resistant to analgesic therapy.⁵ Unrelieved pain is one of the most common causes of functional disability and unnecessary suffering for terminally ill cancer patients.^{6,7} Moreover, opioids can have prohibitive side effects including nausea, vomiting, pruritus, constipation, lethargy, urinary retention, and respiratory depression.

When pain is resistant to standard therapy or when severe side effects of analgesics occur, alternative analgesic techniques should be considered, including spinal analgesics, regional blocks, spinal cord stimulation, vertebroplasty, and neurolytic blocks.⁵ Neurolysis may be accomplished using heat, cryogenic, surgical, or chemical methods.^{8,9} Ethanol (50%–100%) and phenol (carbolic acid) (5%–12%) are the most commonly used neurolytic agents. In terminally ill cancer patients, phenol has been administered using the intrathecal or epidural routes or for blockade of sympathetic ganglia (celiac, superior hypogastric, ganglion impar, etc.).¹⁰ A literature search performed on PubMed and Medline using the keywords “phenol” and “transforaminal” found no references. We are

presenting the first case report using transforaminal phenol injections for treatment of intractable cancer pain.

CASE DESCRIPTION

A 76-yr-old man with Stage IV leiomyosarcoma with multiple metastatic lesions complained of lancinating and unremitting pain in the right thoracic and lumbar regions at rest. The pain severely restricted the patient's ability to lie on his sides, to make any movements, and also to engage in effective communication with his family. Computed tomography and magnetic resonance imaging demonstrated metastatic lesions extending from L1 to S2 invading the epidural space, limiting the central canal to <6 mm. Additionally, a compression fracture from a fall was noted at T9 with metastatic lesions identified in the T9-10 epidural spaces invading the contiguous vertebral bodies. Because of increasing pain, loss of bladder and bowel control, and impending paralysis of the lower extremities, a lumbar laminectomy was performed to decompress an epidural tumor extending from L2-4. Two months later, transpedicular removal of a vertebral body tumor and decompression of the T9 and T10 levels followed. Two weeks after surgery, the pain service was consulted for assistance with palliative care. At that time, the patient's pain regimen included fentanyl patches (450 µg/h), IV patient-controlled analgesia delivering 4 mg of hydromorphone every 10 min, dexamethasone 10 mg every 6 h, hydromorphone 4-mg tablets every 4 h as needed, methocarbamol 500-mg tablets 3 times a day, gabapentin 200-mg capsules every 8 h, and celecoxib 200-mg capsules twice a day. The patient was cognitively impaired and constipation limited his comfort. All movement exacerbated his pain to a level he described as 10/10 on a numeric rating scale. The patient requested “any definitive” treatment for the right-sided thoracic and lumbar pain, which he characterized as stabbing, piercing, and throbbing in nature. A family meeting with the patient present was conducted to discuss phenol neurolysis using a transforaminal approach with emphasis on known risks including spinal cord infarction, bleeding, infection, further spread of the tumor, and death.

The patient was brought into the operating room and was placed prone. Standard American Society of Anesthesiologists monitors were applied and IV sedation was titrated to

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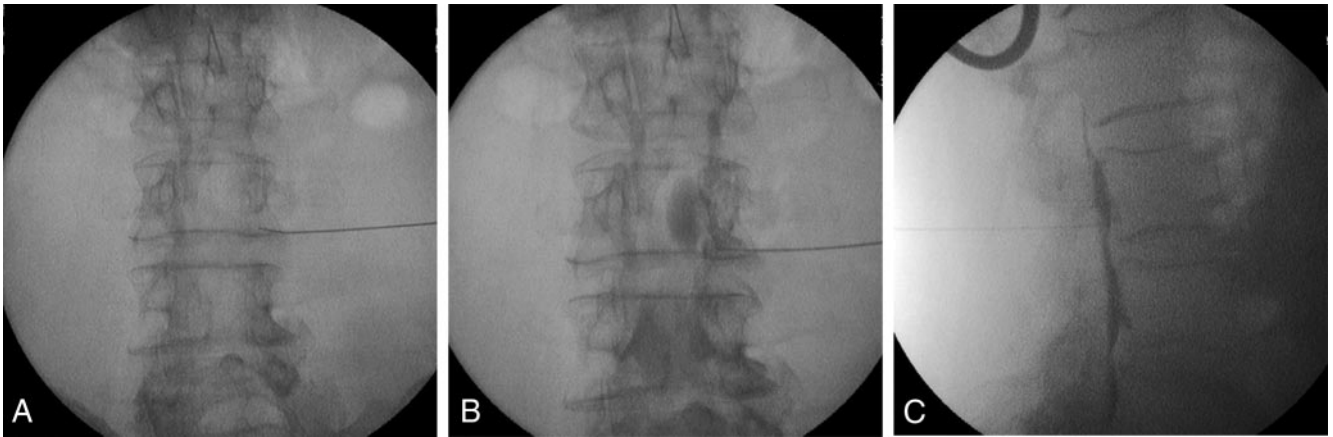


Figure 1. Right L3-4 phenol neurolysis. A, Anterior-posterior fluoroscopic view, a 22-gauge Whitacre subarachnoid needle advanced into the L3-4 neuroforamen under fluoroscopic guidance. B, Anterior-posterior fluoroscopic view. C, Lateral fluoroscopic view. B and C, Demonstrating 3 mL Isovue-200 contrast spread in the peridural space with subsequent neurolysis with 3 mL phenol 5% and glycerin 50%.

allay anxiety while ensuring appropriate feedback to sensory stimuli. The patient's back was prepped and draped in a sterile fashion. The right L3-4 neuroforamen was located using fluoroscopic guidance. A skin wheal was raised using 3 mL of bupivacaine 0.5% via a 25-gauge, 1.5-in. needle. A 22-gauge, 6-in. Whitacre-type subarachnoid needle with a curve at its distal tip was then advanced atraumatically toward the cephalad and dorsal most quadrant of the neuroforamen at L3-4 under continuous fluoroscopy (Fig. 1A). No cerebrospinal fluid, blood, or paresthesias were produced. Three milliliters of Isovue-200 contrast was incrementally injected using continuous, live fluoroscopy, outlining the (presumed) peridural space from L2-4 on the right side (Figs. 1B and C). The L2-4 spread of contrast remained tightly adherent to the posterior longitudinal ligament and approximately corresponded to the patient's expressed level of pain while serving as an estimate to gauge the ultimate equivalent volume of neurolytic drug to use. Next, 3 mL of phenol 5% in glycerin 50% was injected. The needle was flushed with 1 mL of 1% lidocaine and was withdrawn. There were no appreciable changes in heart rate or arterial blood pressure noted, and within 60 min, with the clinical effects of the sedation waning, the patient admitted to substantial pain relief (numerical rating scale 3/10).

Given the favorable, yet incomplete, result with residual right flank, groin, and hip pain, 2 days later phenol neurolysis was planned for the T12-L2 levels using the same methods described above for pain that was cephalad to the area covered by the L2-4 neurolysis. No complications or side effects were noted after the second procedure.

The patient admitted to complete pain resolution and was able to have meaningful contact with family members because he was more lucid. Subsequently, all the above-mentioned medications were discontinued, aside from one 100 $\mu\text{g}/\text{h}$ fentanyl patch to attenuate any withdrawal symptoms. The patient was transferred to hospice care and had considerable contact with extended family members until his death 11 days after the procedure because of extensive metastatic lesions present in both lungs that resulted in respiratory failure.

DISCUSSION

Unrelenting, inadequately controlled pain can be debilitating with severe impairment in quality of life and activities of daily living.³ Despite multimodal approaches to reduce pain, 46% of terminal patients

receive inadequate pain treatment, as reported by family members.¹¹ Cancer pain is frequently insufficiently managed and many patients spend the last days of their lives suffering from unrelieved pain.¹²⁻¹⁴ Implementation of the World Health Organization analgesic guidelines⁴ is useful for managing cancer pain.⁸ However, high doses of opioids can have deleterious side effects including suppression of the cellular immune response.¹⁵ Lillemoe et al.¹⁶ in a randomized prospective study found that patients with pancreatic cancer who underwent splanchnic neurolysis lived longer than patients who received opioids alone, suggesting an improved immune response as the underlying mechanism. With these contingencies in mind, our patient with leiomyosarcoma, including multiple metastatic lesions and unrelieved pain in the right thoracic and lumbar regions, appeared ideal for neurolysis. His pain was uncontrolled despite high doses of opioids. Moreover, his cognitive ability had severely deteriorated. Constipation ensued, complicating his daily life and social interactions. The patient underwent phenol neurolysis using a transforaminal approach, performed in 2 stages at 3 levels (L3-4, L1-2, and T12-L1). Subsequently, there was complete resolution of pain with nearly total ability to discontinue opioid use. Classical epidural approaches were deemed not feasible due to widespread tumor infiltration into that space and due to 2 recent extensive laminectomy procedures. Likewise, subarachnoid techniques (which rely exclusively on the hypo- or hyperbaric properties of the respective neurolytic drug) were excluded due to the patient's inability to lie comfortably on either side for even a brief period of time. That left us with only the transforaminal approach, because his ability to remain prone for the expected duration of the blocks was acceptable.

Phenol (carbolic acid) was introduced in the 1950s¹⁷ and has local anesthetic effects making its injection

less painful than ethanol.⁵ Ethanol is another chemical neurolytic agent¹⁶ and was not chosen in this case because it produces burning sensations in the injected region.⁸ Phenol neurolysis is an effective treatment for managing intractable cancer pain.^{18–21} The use of 10% phenol neurolysis of the superior hypogastric plexus for pelvic pain induced moderate to excellent pain relief in 79% of 227 patients, with a reduction of opioid use by 40%, even reducing opioid consumption in the failure group.¹⁹ Turker et al.²¹ showed that superior hypogastric plexus block using phenol 10% provided significant pain relief lasting from 6 to 12 mo.

Neurolysis is less commonly used for nonmalignant pain because of risks of neurologic deficit, damage to nonneural tissue, and physical incapacity,⁸ although it is listed in the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section as an option.²² The phenol (4%) used for neurolysis in 42 patients with severe nonmalignant pain showed pain relief in 83% of patients (numeric rating scale ≤ 3) with no complications.²³

The presently described patient did not have any complications after transforaminal phenol neurolysis. Although side effects and complications from phenol neurolysis are rare, local and systemic complications can occur. Severe burning pain in the distribution of the nerve has been reported after phenol neurolysis.²⁴ Phenol injected near motor nerves can produce flaccid paralysis.²⁵ Phenol can also cause systemic complications such as nausea, vomiting, central nervous system stimulation, cardiac arrhythmias, respiratory arrest, and paraplegia.^{25–27} Kowalewski et al.²⁷ reported persistent paraplegia as a complication of phenol intercostal neurolysis, resulting from phenol diffusion into the epidural space. Galizia and Lahiri²⁶ reported paraplegia after phenol celiac plexus block as a result of vascular ischemia of the spinal cord. Common to those 2 cases is that both used aqueous phenol solutions (7.5% and 6%). Phenol in combination with 50% glycerin, which we chose, should be considered if an injection needs to be made in an area close to the spine, especially for patients who are already neurologically compromised. Although phenol-glycerin is a very viscous solution and requires administration through larger bore needles,⁹ the relatively higher density may allow the mixture to localize in the dorsal epidural space,²⁰ thus minimizing extension to ventral motor nerve roots. Indeed, while we presumed the epidural space would likely be compromised or even obliterated after 2 recent decompressive laminectomies, we were impressed and surprised to encounter a tight linear spread of contrast (Fig. 1C) that would imply continuity of the posterior longitudinal ligament.

Intractable pain should not be acceptable in terminally ill patients. We describe the first reported transforaminal phenol neurolysis in a patient with intractable cancer pain. Phenol was not only effective in pain relief but also avoided side effects of

opioids and improved the quality of life in this patient. In the rare instance of encountering patients who may benefit from neurolysis, but who have anatomical impediments to peridural approaches (i.e., tumor infiltration, scar tissue, and recent ablative surgery) or subarachnoid techniques (inability to assume a lateral decubitus posture), we believe that transforaminal placement of neurolytic drugs offers a viable and practical alternative.

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Spinal Cord Stimulation for Severe Degenerative Joint Disease of the Shoulder in a Patient with Severe Chronic Obstructive Pulmonary Disease: A New Indication?

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Approximately 70% of the United States population older than 65 yr has osteoarthritis. Chronic obstructive pulmonary disease (COPD) is also more prevalent in the elderly, and thus, the likelihood of having elderly patients with osteoarthritis and COPD in clinical settings is significant. COPD may preclude the optimum use of opioids, thus the potential to provide pain control with nonpharmacological treatment modalities becomes a valuable option. We present the case of an elderly woman with severe degenerative joint disease of the shoulder and severe COPD in whom spinal cord stimulation was used to provide pain control.

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Osteoarthritis (OA) and chronic obstructive pulmonary disease (COPD) afflict a significant proportion of elderly patients.¹⁻³ Individuals who present with OA and COPD pose a clinical challenge fraught with the need to balance the potential benefits of opioid therapy with the risks of respiratory depression. We report a case in which spinal cord stimulation (SCS) was successfully used to treat a patient with severe shoulder degenerative joint disease (DJD) and COPD. Because the patient could not tolerate the prone position because of severe COPD, the trial lead was placed in the sitting position. This case is unique because it represents the first published report whereby SCS provided long-term benefit in a patient with shoulder DJD, a classical nociceptive pain condition, and contains the first description detailing trial lead placement in the sitting position in a patient unable to tolerate recumbency because of severe COPD.

CASE DESCRIPTION

A 67-yr-old woman presented to the orthopedic surgeon with right shoulder pain secondary to DJD. Her right shoulder radiograph confirmed the presence of severe shoulder arthritis and revealed glenoid bone loss, joint space obliteration, with evidence of chronic rotator cuff disease. Her medical history was significant for debilitating COPD

with a 100 pack/yr smoking history, kyphoscoliosis, and peripheral vascular and coronary heart disease. Her surgical history was significant for left shoulder arthroplasty, multiple cerebral aneurysm clippings, and a right subclavian artery bypass performed a year before the current presentation complicated by right-sided phrenic nerve injury and associated right hemidiaphragmatic dysfunction. Her pulmonary workup revealed moderately severe obstructive and restrictive lung disease and evidence of a reduced right hemidiaphragmatic excursion with associated 3-pillow orthopnea at baseline. Pulmonary function tests revealed forced expiratory volume (FEV) 1.06, FEV₁/forced vital capacity 70.7, predicted 78.4; total lung capacity 2.93, predicted 4.17; carbon monoxide diffusing capacity 6, predicted 15.7; arterial blood gas sampling revealed pH 7.41, Pco₂ 39, and O₂ saturation of 90% on 1-2 L/min of oxygen.

A preoperative evaluation was performed by her pulmonologist, cardiologist, and vascular surgeon who performed the subclavian artery bypass. Considering her medical history and the potential risk to the subclavian graft during the shoulder arthroplasty, the patient was deemed a poor surgical risk. She was started on sustained-release oxycodone 10 mg once per day to minimize the risk for respiratory depression. Subsequent attempts at dose escalation had resulted in respiratory depression with modest associated pain relief. Because of suboptimal analgesia at the tolerated dosage of an opioid analgesic, she was subsequently referred for a SCS trial.

At trial, the patient was placed in the prone position with supplemental oxygen at 6 L/min. Within minutes, she became dyspneic, with her oxygen saturation decreasing to 87%. She was repositioned to the sitting position, after which her symptoms resolved. A second attempt was made with the same result. After further discussion, a decision was made to proceed with percutaneous implantation in the sitting position.

Access to the epidural space was achieved using a 14-gauge Tuohy needle. An SCS trial lead (Octrode lead, Advanced Neuromodulation Systems®, Plano, TX) was then threaded to the C3 level under fluoroscopic guidance. Paresthesias encompassing the right shoulder and arm were noted, with the patient reporting a significant decrease in pain.

During the week-long trial period, the patient reported 75% pain relief. Five weeks later, a permanent SCS paddle

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Figure 1. Radiograph demonstrating the permanent cervical spinal cord stimulation lead, previous left shoulder arthroplasty, degenerative joint disease of the right shoulder, and an elevated right hemidiaphragm.

lead was placed via a laminotomy performed under general anesthesia (Lamitrode lead, Advanced Neuromodulation Systems; Fig. 1). Eighteen months after the implant, she reported 50% pain relief and took only tramadol “as needed.”

DISCUSSION

The treatment for OA depends on the joint(s) involved but typically involves pharmacotherapy, corticosteroid injections, and/or viscosupplementation. Joint replacement is the treatment of choice in severe shoulder OA. However, this patient was deemed to be a poor surgical candidate primarily because the proximity of a right subclavian graft to the surgical site would have placed it at risk for damage during surgical exposure of the right shoulder. Her coexisting medical conditions were also a consideration for increased anesthetic risk.

The rationale to proceed with the SCS trial was based on the patient’s inability to tolerate opioids at a dosage that diminished pain and the possible risk posed by polypharmacy in this patient population.⁴ A possible explanation for the beneficial effect of SCS in DJD was postulated by Schaible and Grubb,⁵ whose model depicts the spinal cord as the center for the integration of afferent information. They speculated that functional central neuroplasticity in arthritis contributes to the neuronal events associated with inflammation.⁵ Schaible et al.⁶ later postulated that inflammation of joints results in peripheral and central

sensitization, which is a significant component of arthritic pain. They surmised that in a positive feedback loop, sensitization is the means through which the nervous system influences the inflammatory process.

However, given that this response was observed in a single case, no deductions can be made as to the exact mechanism of action in this case. The possibility of the placebo effect cannot be excluded because there was no control against which to compare the effects of sham stimulation. In an effort to mitigate this shortcoming, we asked the patient to switch off the stimulator for several days at a time and she reported exacerbation in her baseline pain, which subsided after switching on the SCS.

The need to place our patient in the sitting position was prompted by her inability to tolerate the prone position because of pulmonary dysfunction. During the SCS trial, the patient obtained significant pain relief and was able to discontinue the extended release oxycodone after permanent implantation. At her most recent follow-up, she continued to experience 50% pain relief. However, it must be noted that although this patient represents a case in which opioids were not tolerated, a significant number of patients with COPD and chronic pain are managed successfully with opioids.

In summary, this case depicts the dilemmas posed when treating chronic pain patients with medical conditions that preclude the use of high-dose opioids. It will hopefully provide the impetus for further study of SCS in this growing population.

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The Assessment of Cold Hyperalgesia After an Incision

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BACKGROUND: Although cold hypersensitivity is a well-documented phenomenon in animals and humans with inflammatory and neuropathic pain, little is known about the presence of cold hyperalgesia after surgery. Therefore, we studied primary cold hyperalgesia after a surgical incision in mice.

METHODS: Before and after plantar incision, inflammation with complete Freund adjuvant, and spared nerve ligation, unrestrained male animals were placed on a Peltier-cooled cold plate with a surface temperature of 0°C and withdrawal latencies were measured. Additionally, incision-induced cold hyperalgesia was also assessed in female animals. Furthermore, skin temperature before and after plantar incision and inflammation were assessed by using infrared thermography (Varioscan LW 3011; Infratec, Dresden, Germany).

RESULTS: Cold hyperalgesia to a noxious cold stimulus was observed after inflammation and nerve injury but not after a surgical incision. Similar results were demonstrated for female animals after incision. Furthermore, a significant increase in skin temperature was recorded after inflammation but not after incision, indicating that a surgery evokes only minor inflammatory effects.

CONCLUSION: The present data give strong evidence that a surgical incision does not cause cold hyperalgesia. Furthermore, a lack of cold hyperalgesia in unrestrained male and female mice after incision was not due to increased skin temperature after incision. Finally, we demonstrated that in contrast to a surgical incision, inflammation and nerve injury generate intense cold hyperalgesia and an increase in skin temperature, suggesting that different mechanisms are involved in surgical and inflammatory or neuropathic pain.

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For animals and humans, the transduction of cold sensation is an important aspect of neurophysiology. Depending on stimulation intensity and degree of cold temperatures, cooling the skin evokes either innocuous or noxious sensations. Considerable evidence indicates that nonpainful cool sensation and cold pain are mediated by separate populations of primary afferent fibers. Although cold-specific A- δ and C fibers with discharge rates mostly restricted to cold temperatures between 20°C and 30°C are important for the signaling of innocuous cool sensation, only a subpopulation of nociceptors is excited by noxious cold.¹⁻³ Different cold transducers including TRPM8 and TRPA1, both members of the transient receptor potential (TRP) ion channel superfamily, seem to contribute to cool

versus noxious cold sensation. TRPM8, largely expressed in TRPV1-negative small afferents, detects innocuous cooling, whereas TRPA1, expressed in peptidergic TRPV1-positive nociceptors, is most likely responsible for detection of noxious cold and contributes to cold hypersensitivity after tissue injuries.^{4,5}

Cold hypersensitivity is a well-documented phenomenon that occurs in animals and humans with inflammatory and neuropathic pain.⁴⁻⁶ Cold hyperalgesia has been reported in 9% of patients with neuropathies and 23% of patients with poststroke central pain.^{5,7,8} However, little is known about the presence of cold hyperalgesia after surgery, and the results of the existing studies are contradictory. Stawowy et al.⁹ reported a lack of referred cold hypersensitivity in patients after cholecystectomy. In agreement, an incision of the medial thigh with tissue retraction in rats did not cause secondary cold hyperalgesia.¹⁰ In contrast, primary cold hypersensitivity has been reported after plantar incision in the rat by dipping the foot in a cold water bath.¹¹

Therefore, the primary aim of this study was to assess cold hyperalgesia after a surgical incision in unrestrained male and female mice using a Peltier-cooled cold plate. Furthermore, we compared the occurrence of cold hypersensitivity among a surgical incision, peripheral inflammation, and a nerve injury, and evaluated the skin temperature after plantar incision and inflammation by using infrared thermography.

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METHODS

General

These experiments were reviewed and approved by the institution's Animal Care and Use Committee (Muenster, Germany). The animals were treated in accordance with the Ethical Guidelines for Investigations of Experimental Pain in Conscious Animals as issued by the International Association for the Study of Pain.¹² Experiments were performed on 54 adult male mice and 12 female C57BL/6NHsd mice (weight 20–25 g; Harlan Winkelmann, Borcheln, Germany). Food and water were available *ad libitum*. Postoperatively, the animals were housed individually. Seven animals were excluded for wound dehiscence; at the end of the protocol, all animals were anesthetized and killed with an overdose of potassium chloride administered intracardially.

Different Types of Tissue Injuries

For paw incisions, all mice were anesthetized with 1.5%–2% isoflurane delivered via a nose cone. As described previously,¹³ a 0.5-cm longitudinal incision was made through skin and fascia of the plantar aspect of the right hindpaw. The skin was apposed with 1 mattress suture of 5-0 nylon. After surgery, the animals were allowed to recover in their cages. Sutures were removed approximately 30 h later at the end of postoperative day 1, and the wounds healed well within 5–6 days.

Inflammation was elicited in anesthetized mice (isoflurane anesthesia) by intraplantar injection of complete Freund adjuvant (CFA) (20 μ L; Sigma, Aldrich, Germany) using a 27-gauge needle.

Neuropathic pain was induced by using the spared nerve injury model for mice described previously.¹⁴ Briefly, mice were anesthetized with isoflurane and 3 terminal branches of the sciatic nerve were exposed through an incision of the skin and muscle at the lower thigh. Subsequently, the common peroneal and sural nerves were tightly ligated with 7-0 silk and transected distal to the ligation, leaving the tibial branch intact. The wound was closed and the animals were allowed to recover.

Pain Behaviors

Before experiments were started, the mice were adapted to the testing conditions. On the day of the experiment, the temperature of the cold plate was set to 0°C, and mice were placed individually onto the cold plate. Subsequently, time was recorded until a brisk lift of the right hindpaw occurred. This test was repeated 3 times and the average time of the 3 tests was interpreted as the latency for cold pain withdrawal. A maximum cutoff time of 60 s was used to prevent tissue damage.

Experimental Protocols

Twenty male mice were pretested for cold-evoked pain behaviors as described above. Subsequently, a

sham preparation ($n = 10$) or the incision ($n = 10$) was made in the plantar aspect of the foot, and after a recovery time of 2 h, cold hypersensitivity was assessed on the day of surgery and for the next 4 wk. Because Kwan et al.¹⁵ reported a gender-dependent sensitivity to noxious cold stimulation (female > male), we assessed cold-evoked pain behaviors after incision and sham preparation in a separate group of female mice ($n = 6$ each group; data not shown).

In separate groups of animals, cold hypersensitivity was tested after intraplantar injection of CFA (inflammation; $n = 12$) or spared nerve injury (SNI) (neuropathic pain model; $n = 8$) for 60 and 21 days, respectively.

Temperature Measurement of the Mouse Hindpaw Skin

Because cutaneous temperature abnormalities after tissue injury may change the development of cold hypersensitivity, we assessed skin temperature before and continuously after sham preparation ($n = 4$), incision ($n = 5$), and inflammation ($n = 5$) with infrared thermography.¹⁶ The infrared radiation, transmitted to both plantar hindpaws of unanesthetized restrained mice, was recorded by a liquid nitrogen-cooled infrared sensor camera (Varioscan LW 3011; Infratec, Dresden, Germany) with a temperature resolution of 0.03°C. Thermal images were obtained at 0 (before inflammation or incision), 2, 4, and 6 h, and daily on Days 2–7 after intraplantar CFA administration or incision. The acquired images were saved by a computer system, a region of interest from the ankle to the pads of the plantar hindpaw was drawn, and average temperature of all pixels within the region of interest of each image was analyzed offline by a blinded investigator using custom-made software (IRBIS Plus 2.2; Infratec).

Statistical Analysis

The results are presented as mean with standard deviation, and all data were compared using parametric analyses including 1-way analysis of variance for within- or between-group comparisons and unpaired *t*-test. Multiple comparisons after analysis of variance were performed using a Dunnett test. $P < 0.05$ was considered significant. Data were analyzed using Prism software (Version 5.02; GraphPad, San Diego, CA).

RESULTS

Cold Hyperalgesia After Incision, Inflammation, and SNI

In male mice with a plantar incision and sham preparation, average noxious cold withdrawal latency was 55 ± 5.1 s before surgery and remained above 50 s throughout the entire observation period (Fig. 1A). Similar results were observed in female mice after incision and after sham preparation (data not shown).

In contrast, mean noxious cold withdrawal latencies decreased significantly from 55.4 ± 6 s before injection of CFA to mean withdrawal latencies between 30 and 40 s for several days afterward (Fig. 1B).

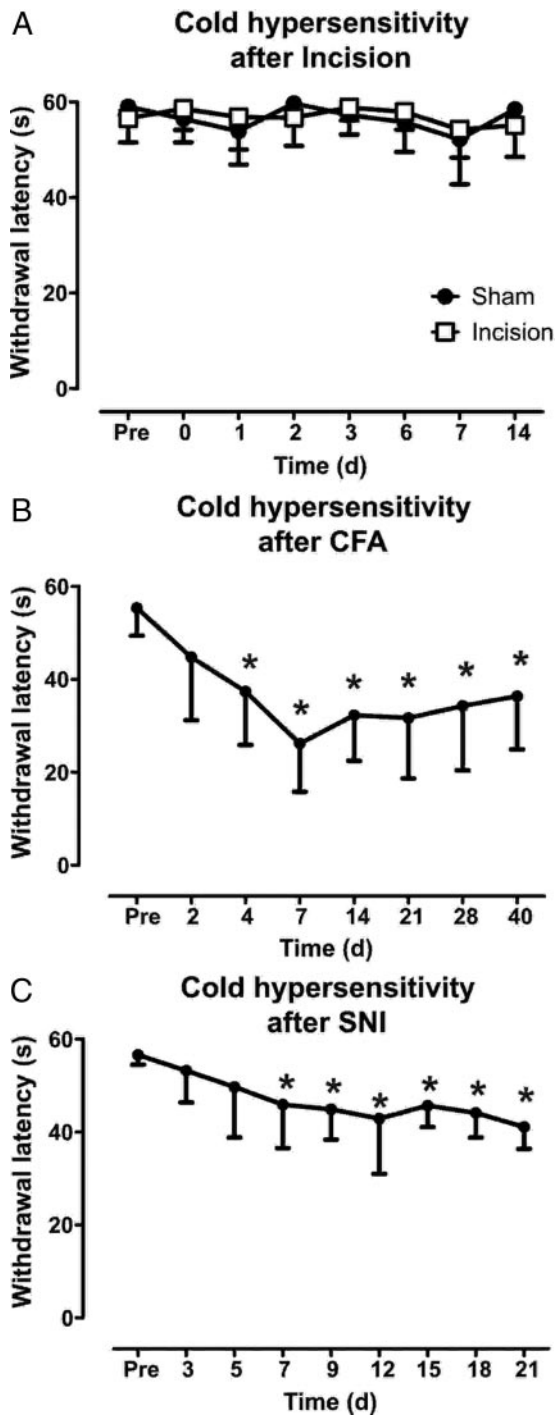


Figure 1. Primary cold hypersensitivity. A, Lack of cold hypersensitivity in sham-operated animals and after an incision. B and C, Significant cold hypersensitivity in animals after inflammation with complete Freund adjuvant and after spinal nerve injury (SNI). * $P < 0.05$ vs 0 h or vs control (incision). The symbols represent the mean \pm SD.

Similarly, we observed a moderate but significant decrease of noxious cold withdrawal latencies from 56.6 ± 2.1 s before SNI to average withdrawal latencies below 47 s 7 days after nerve injury (Fig. 1C).

Cutaneous Temperature of the Mouse Hindpaw After Incision and Inflammation

In male mice, the average cutaneous hindpaw temperature was $24^\circ\text{C} \pm 0.6^\circ\text{C}$ before incision and stayed

between 24°C and 25°C throughout the entire experiment, indicating that a possible incision-induced cold hypersensitivity was not occluded by increased skin temperature (Fig. 2). In contrast, average cutaneous hindpaw temperatures significantly increased from $23.5^\circ\text{C} \pm 0.2^\circ\text{C}$ before CFA injection to 27°C – 29°C 1–5 days after induction of inflammation with CFA ($P < 0.05$ vs 0 h and vs control). These data indicate that inflammatory processes important for an increase of skin temperature may play an important role for inflammatory but not incision-induced pain behavior.

DISCUSSION

In this study, we demonstrated for the first time that a surgical incision does not cause primary noxious cold hyperalgesia in unrestrained male and female mice. Furthermore, we observed only minor changes in cutaneous hindpaw skin temperature, indicating that incision-induced cold hyperalgesia was not concealed by an increase in skin temperature. Finally, we demonstrated that in contrast to a surgical incision, inflammation caused by CFA injection generated intense and long-lasting cold hyperalgesia and an increase in skin temperature, suggesting that different mechanisms are involved in surgical and inflammatory pain.

Cold Hyperalgesia After Different Types of Tissue Injury of Acute and Persistent Nociception

Cooling the skin to innocuous cool temperatures of 15°C – 30°C or to noxious cold at 15°C and below evokes nonpainful cool sensations and cold pain, respectively. Innocuous cool sensation is mediated by cold-specific A- δ and C fibers and at least partly by the activation of TRPM8 receptors.^{1–3} Cold pain is mediated by a distinct subpopulation of nociceptors and possibly by the activation of TRPA1 and TRPM8.¹⁷ Considerable evidence, including this study, indicates that peripheral inflammation induces cold allodynia (nonpainful cool sensations) and cold hyperalgesia.⁶ This occurs despite an increase in foot surface temperature between 2°C and 7°C .¹⁸

Cold allodynia and/or cold hyperalgesia are also present in patients who have a variety of neuropathies and poststroke central pain.^{5,7,8} Furthermore, several researchers conducting experimental studies using different models of neuropathic pain, including the spinal nerve ligation model and the SNI model, observed cold allodynia.⁶ However, Allchorne et al.⁶ reported cold hyperalgesia only after SNI but not after spinal nerve ligation. Similarly, we demonstrated in this study a significant decrease in withdrawal latency to noxious cold after spinal nerve ligation.

Little is known about the presence of cold allodynia and/or cold hyperalgesia after a surgical incision. Stawowy et al.⁹ investigated cold hyperalgesia in a referred pain area in patients after open or laparoscopic cholecystectomy. Although most of the patients with acute

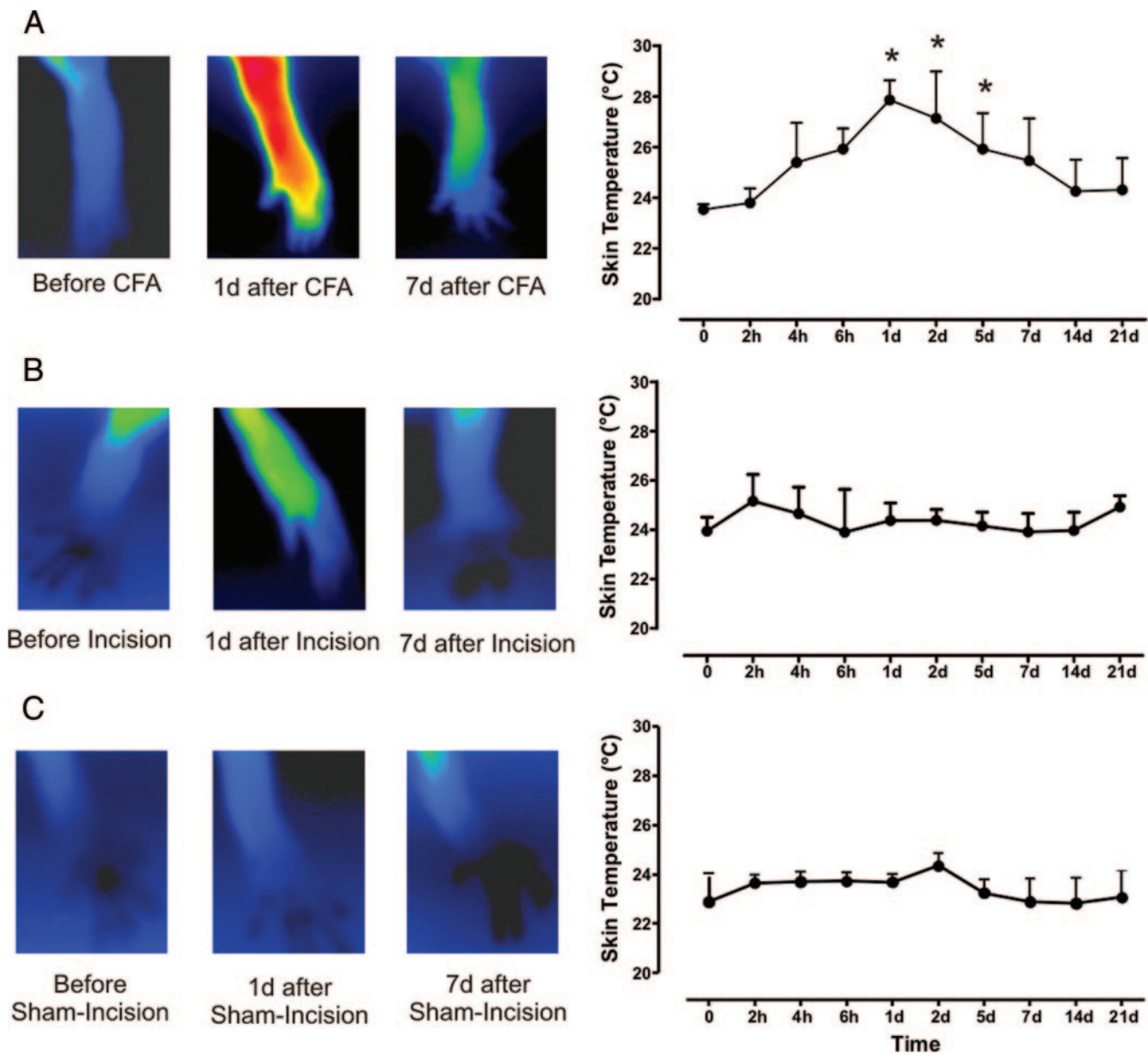


Figure 2. Skin temperature of the mouse hindpaw after incision and inflammation. A, Intense increase of skin temperature 1–5 days after inflammation with complete Freund adjuvant and an example of thermal images before inflammation and 1 and 7 days after inflammation. B, Lack of a significant increase of skin temperature in animals after incision or after sham operation and an example of thermal images before sham operation or incision and 1 and 5 days later. * $P < 0.05$ vs 0 h or vs control (incision). The symbols represent the mean \pm sd.

cholecystitis reported cold hyperalgesia before the surgery, no additional referred cold hypersensitivity was observed after the intervention, indicating that even a large surgical incision with deep tissue injury did not cause referred cold hypersensitivity to a noxious cold stimulus (0°C). Accordingly, in a recent animal experimental model of persistent postoperative pain, an incision of the medial thigh with tissue retraction for 1 h did not cause secondary cold hyperalgesia.¹⁰

In contrast, Singh et al.¹¹ observed primary cold allodynia after a surgical incision in rats by dipping the foot in a 10°C cold water bath, an innocuous cold stimulus. However, the cold water bath test has several limitations. Dipping the hindpaw of a restrained animal into a cooled water bath causes a high level of

stress, which may have nociceptive effects that will confound the interpretation of any behavioral reflex responses.^{6,19} Furthermore, placing the recently incised hindpaw in water may cause a permeation of the liquid in the fresh wound and generate burning pain independent of the temperature. Finally, the study investigated only the presence of cold allodynia (innocuous cold stimulus) but not of cold hyperalgesia after incision.

In a preliminary study, we investigated cold hypersensitivity after incision by recording the duration of pain behaviors caused by the application of a droplet of acetone and observed inconclusive and inconsistent results. One reason for this inconsistency may be a possible permeation of the acetone into the wound

generating burning pain independent of the cool temperature. Furthermore, after application of acetone, only innocuous skin temperatures of more than 15°C were reached, indicating that the acetone paradigm tests only for cold allodynia and not cold hyperalgesia.^{4,20} Therefore, we investigated primary cold hyperalgesia after a surgical incision in unrestrained mice using a Peltier-cooled cold plate with a low surface temperature of 0°C (noxious cold stimulus). In the manner of Allchorne et al.,⁶ we measured the latency to the first hindpaw withdrawal rather than a cumulative response to a fixed time to limit the exposure of the animals to the cold surface (0°C) and to avoid possible skin damage.

One reason for a lack of cold hyperalgesia after incision could be an increase of skin temperature after surgery, which enhances the gradient between cold receptor threshold and skin temperature and may mask a decreased withdrawal latency to a noxious cold stimulus. Similarly, Liang et al. demonstrated that heat thresholds of sensitized nociceptors during inflammation were near body temperature, indicating that modification of skin temperature may be critical for increasing (skin temperature above threshold) or decreasing (skin temperature below threshold) inflammatory-induced pain.^{21,22} Therefore, we measured skin temperature using infrared thermography and demonstrated only a brief and minor increase in skin temperature, indicating that a modification in skin temperature did not mask putative incision-induced cold hyperalgesia. Additionally, the lack of a significant increase in skin temperature after incision suggested only a minor inflammatory component of postsurgical pain and emphasized that inflammatory and incisional pain are mediated by different mechanisms. Although there is ample evidence of an upregulation of inflammatory mediators including prostaglandin E2 at the surgical site,²³ it is not clear whether the mediator concentration in the wound is sufficient to induce nociceptor sensitization and inflammation. Further studies are needed to clarify the role of peripheral inflammation for postoperative pain. Another reason for a lack of cold hyperalgesia after incision might be a gender-dependent effect for the appearance of cold hypersensitivity. Kwan et al.¹⁵ reported that wild-type female mice are more sensitive to noxious cold stimulation, but not to moderate cooling, than male animals. Therefore, we also tested pain behavior to noxious cold stimulation after incision in female mice and did not observe a statistically significant decrease in withdrawal latencies, indicating that a gender-dependent difference in cold hyperalgesia was not responsible for the lack of cold hyperalgesia after incision.

Importantly, the lack of cold hyperalgesia after incision has to be distinguished from a potential antinociceptive effect of mild skin cooling.^{4,5} There is considerable evidence that wound cooling reduced opioid requirements and decreased pain scores after

knee arthroplasty,²⁴ hernia repair,²⁵ and spinal surgery.²⁶ The physiological effects of mild cooling include inhibited induction of inflammation and edema formation because of reduced blood circulation and tissue metabolism, decreased muscle spasm, and direct local analgesia caused by slowed nerve conduction velocity.²⁵ However, the detailed molecular mechanisms of cooling-induced analgesia are largely unknown. Recent animal experimental research demonstrated that cooling-induced analgesia was mediated in part by the activation of the TRPM8 receptor. Thus, current evidence suggests that TRPA1 is primarily responsible for cold hypersensitivity, whereas TRPM8 appears to mediate cooling-induced analgesia.^{4,5}

CONCLUSION

In this study, we demonstrated for the first time that a surgical incision does not cause primary noxious cold hyperalgesia in unrestrained male and female mice and that a lack of cold hyperalgesia is not caused by increased skin temperature after incision. Finally, we demonstrated that in contrast to a surgical incision, inflammation generates intense and long-lasting cold hyperalgesia and an increase in skin temperature, suggesting that different mechanisms are involved in surgical and inflammatory pain.

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The Effects of Resiniferatoxin in an Experimental Rat Thoracotomy Model

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BACKGROUND: Chronic pain after thoracotomy has been reproduced in a rat model that allows investigation of drugs that might reduce the incidence of allodynia after thoracotomy. Previous studies suggest that morphine, clonidine, neostigmine, gabapentin, and bupivacaine reduce the incidence of allodynia in the rat postthoracotomy pain model. One purpose of this study was to test whether intercostal injection of resiniferatoxin (RTX) decreased the amount of allodynia in an animal model of chronic postthoracotomy pain. We also tested whether RTX induced a transient mechanical hyperalgesic response in uninjured animals.

METHODS: Male Sprague-Dawley rats were anesthetized, and the right fourth and fifth ribs were surgically exposed. The pleura was opened, and the ribs were retracted. Intercostal RTX 0.8 or 8 μ g was injected in animals that developed allodynia after surgery; a control group underwent rib retraction and received vehicle only. An additional group of uninjured animals received RTX. Rats were tested for mechanical allodynia at a predetermined area around the incision site for 3 wk.

RESULTS: Allodynia developed in 42% of the animals that underwent thoracotomy. A transient hyperalgesic response was noted in the uninjured group that underwent drug injections. Intercostal RTX did not modify the course of allodynia in injured rats.

DISCUSSION: The current results suggest that intercostal RTX causes a transient hyperalgesic response in uninjured animals and is ineffective in reducing the mechanical allodynia after thoracotomy.

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Lung cancer is the leading cause of cancer death in the United States,¹ and patients who have a relatively positive prognosis are usually candidates for surgery that often involves either thoracotomy or video-assisted thoracoscopic surgery. Chronic postthoracotomy pain (CPTP) is defined as "pain that recurs or persists along a thoracotomy incision at least 2 mo after the surgical procedure."² CPTP is typically described as a continuous dysesthesia with burning and aching in the general area of the surgical incision that affects up to 55% of patients.^{3,4}

Chest wall resection and pleurectomy seem to increase the likelihood of chronic pain compared with pulmonary resection alone.⁵ In contrast, the muscle-sparing thoracotomy approach⁶ and the use of video-assisted thoracoscopic surgery⁷ may decrease the incidence of chronic

pain and disability compared with conventional thoracotomy. The combined use of intraoperative and postoperative epidural analgesia was found to dramatically decrease the incidence of pain at 6 mo.⁸

Functional impairment and anatomical damage of the intercostal nerves are leading factors in the development of this pain syndrome. Rogers et al.⁹ have shown that rib retraction alone caused 50% conduction block in the intercostal nerves on both sides of the retractor in almost every patient who underwent thoracotomy. Buvanendran et al.¹⁰ developed a postthoracotomy pain model in which nearly 50% of the animals developed allodynia and all showed extensive axon loss in the intercostal nerves of the retracted ribs.

Resiniferatoxin (RTX), a very potent vanilloid receptor agonist molecularly analogous to capsaicin that causes a slow and sustained activation of the transient receptor potential vanilloid 1 (TRPV-1) receptor,¹¹ has generated controversy regarding its application in the treatment of chronic pain. First, although RTX was shown to reduce mechanical allodynia in an animal model of chronic neuropathic pain,¹² it has also been shown to be ineffective in another animal model of chronic pain caused by nerve damage.¹³ We hypothesized that RTX injected close to the intercostal nerve reduces the mechanical allodynia in the postthoracotomy pain animal model, assessed by mechanical threshold testing with von Frey filaments in a 3-wk time frame. The implication would be a potential

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human clinical study of RTX evaluating pain reduction after CPTP. Second, conflicting data regarding a transient mechanical hyperalgesic¹⁴ or hypoalgesic response¹⁵ have been associated with RTX administration in animals. We hypothesized that intercostal RTX injected in uninjured animals elicits a transient hyperalgesic response in the area of intercostal injections. The implication of the findings related to this hypothesis is a potential concomitant administration of local anesthetics along with vanilloid agonists¹⁶ to avoid the transient allodynic response that might occur after RTX injections.

METHODS

After obtaining approval from the Harvard Medical Area Standing Committee on Animals (Boston, MA), 71 male rats (Harlan Sprague-Dawley) weighing 280–340 g at the time of injection and surgery were studied. Animals were purchased from Charles River Laboratory (Wilmington, MA) and kept in the animal housing facilities at Brigham and Women's Hospital, with controlled relative humidity (20%–30%), at room temperature (24°C), and under a 12 h–12 h light-dark cycle, with free access to food and water. Rats were handled before the procedure to familiarize them with the experimental environment and to minimize stress-induced analgesia.

Surgical Procedures

Rats were briefly anesthetized with sevoflurane (1%–2% in oxygen) before receiving intraperitoneal xylazine (1.5 mg/kg) and ketamine (4 mg/kg). Animals were then tracheally intubated (16-gauge, 51-mm Teflon IV catheter; Terumo Medical, Somerset, NJ) and connected to a ventilator (model 683, Harvard Instruments, Holliston, MA) for the entire duration of the surgical procedure. A 3-cm incision was made in the skin of the right lateral chest wall between the fourth and fifth ribs. The deep and superficial muscles covering the ribs were retracted to expose the intercostal muscle. A 1.5-cm incision was made in the intercostal muscle and pleura above the fifth rib. The blunt tines of a small self-retaining retractor (model SU-3146, Mueller, McGaw Park, IL) were coated with lubricant (Surgilube) and placed under the fourth and fifth ribs. The retractor was opened to its third position, producing a rib separation of 8 mm, and was left in place for 60 min, as previously described.¹⁰ After the retraction period, the retractor was returned to the closed position and removed. Both the fourth and fifth ribs were approximated and ligated tightly with 3-0 chromic gut sutures. Air was aspirated from the pleural cavity with a 5-mL syringe attached to the tubing to restore normal intrapleural pressure. The superficial muscle covering the ribs was then apposed with 3-0 chromic gut sutures, and the skin was closed with 3-0 nylon sutures. The animals were allowed to recover, and the endotracheal catheter was removed once spontaneous breathing was reestablished.

Procedure for Intercostal Nerve Blocks

All rats were briefly anesthetized with sevoflurane (1%–2% in oxygen) for the duration of the nerve blocks. A 3-cm incision was made in the skin of the right lateral chest wall between the right fourth and fifth ribs. The ribs were retracted to expose the intercostal muscle. After the third, fourth, fifth, and sixth ribs were identified, 0.2 mL of vehicle or RTX was injected close to each intercostal nerve. The superficial muscle covering the ribs was apposed with 3-0 chromic gut sutures, and the skin was closed with 3-0 nylon sutures. The animals were allowed to recover.

Experimental Protocol

The study was divided into 2 different experiments. The first experiment included 3 groups of animals that underwent thoracotomy and developed allodynia (21 of 50). These animals received intercostal vehicle or RTX, 0.8 or 8 μ g ($n = 7$ per group). The second experiment comprised 3 groups of rats without thoracotomy that received intercostal vehicle or RTX, 0.8 or 8 μ g ($n = 7$ per group). Behavioral testing was always performed between 9 and 12 AM at the following time points in injured animals: 1 day before and 1, 3, 6, 9, 12, 15, 18, and 21 days after surgery. Uninjured animals were tested 1 day before and 1, 3, 6, 9, 12, 15, 18, and 21 days after RTX injections. In addition, all animals were tested 2 h after the drug or vehicle administration. For testing, rats were placed in individual semiopen plastic boxes, which allowed access to their chest wall, and were allowed to explore and groom until they settled. A series of calibrated von Frey filaments (Stoelting, Wood Dale, IL) with bending forces ranging from 0.2 to 15.1 g were applied perpendicularly to the dorsal skin surface (corresponding to the estimated T4–5 dermatomes, i.e., <2 cm from the incision) of the chest wall around the incision site with enough force to bend the filament for 6 s. Escape behavior or scratching of the dorsal right upper back skin with the hindpaw within 6 s of the application of a filament was considered a positive response.¹⁰ In the absence of a response, the filament of next greater force was applied. In the presence of a response, the filament of next lower force was applied. The tactile stimulus producing a 50% likelihood of withdrawal was determined using the up-down method, as previously described.¹⁷ Each trial was repeated twice at approximately 2-min intervals, and the mean value was used as the withdrawal threshold. Mechanical allodynia was defined as at least a 20% decrease from the baseline in withdrawal threshold at any time during the experiment, and its persistence at Day 21 after the injury was considered the outcome variable.

In addition, to exclude any RTX effect on the central nervous system, rats were observed for abnormal signs such as sedation, altered grooming patterns, and exploratory behaviors throughout the experiment.

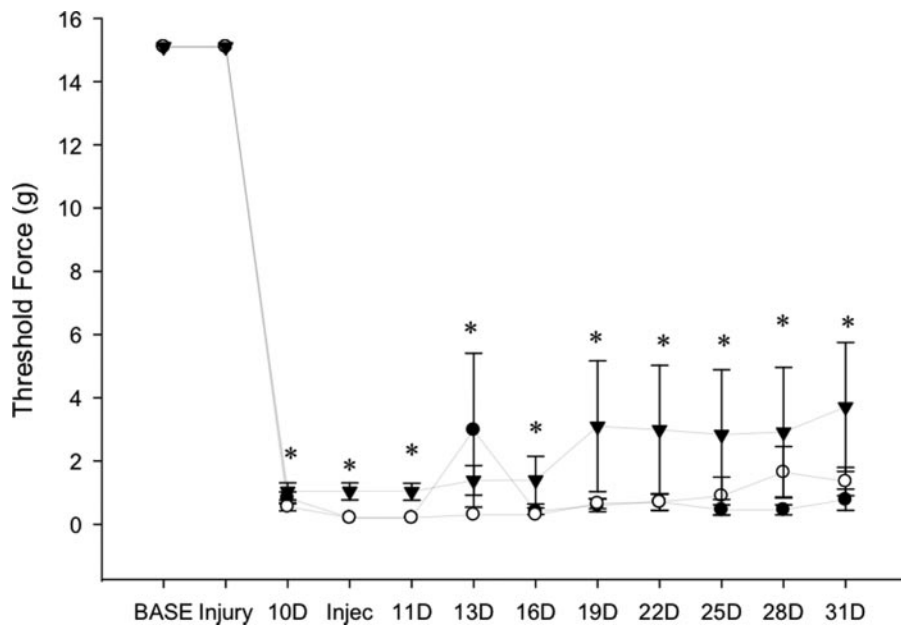


Figure 1. Withdrawal thresholds in injured animals. All groups underwent baseline behavioral testing 1 day before the injury. Animals started to show a decrease in withdrawal thresholds 10 days after injury. Regardless of the treatment received (∇ vehicle, \circ resiniferatoxin 0.8 μg , \bullet resiniferatoxin 8 μg), animals failed to show an increase in withdrawal thresholds in the following 3 wk. Each data point represents the mean \pm SE of the mean. * $P < 0.05$ compared with baseline thresholds.

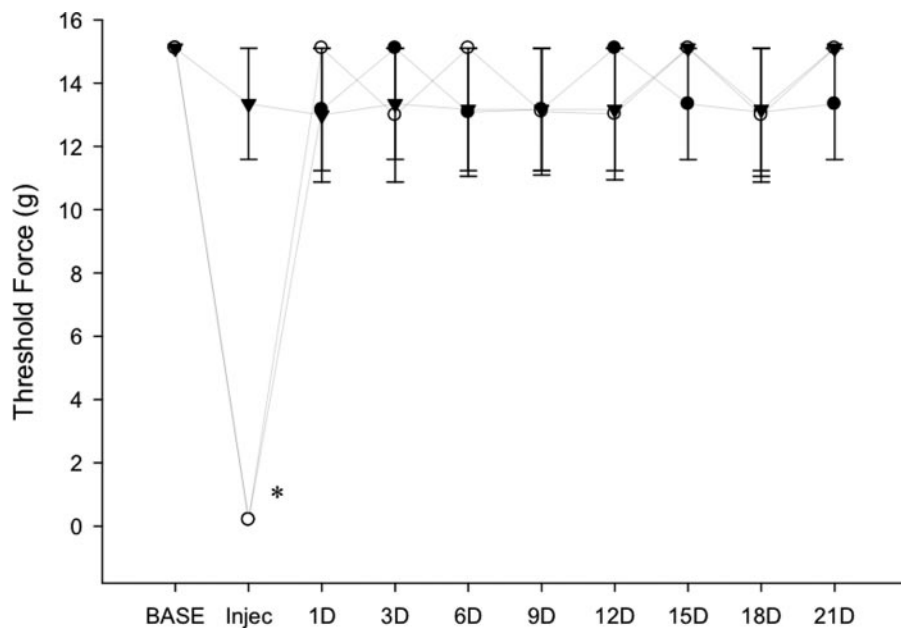


Figure 2. Withdrawal threshold in uninjured animals. All groups underwent behavioral testing 1 day before the injection (∇ vehicle, \circ resiniferatoxin 0.8 μg , \bullet resiniferatoxin 8 μg). Animals injected with resiniferatoxin showed a significant decrease in withdrawal threshold that went back to baseline values the following day. Each data point represents the mean \pm SE of the mean. * $P < 0.05$ compared with the baseline thresholds and with the vehicle-injected group.

Drugs

RTX (Sigma) was dissolved in dimethyl sulfoxide (Sigma, St. Louis, MO) to a concentration of 1 $\mu\text{g}/\mu\text{L}$ and stored at -80°C under nitrogen. It was diluted to 0.0001% or 0.001% in 0.9% saline with 0.3% Tween 80 (to avoid precipitation) to obtain 0.8 or 8 μg , respectively, before being administered to animals in a total volume of 0.8 mL per animal. Because 4 intercostal nerves were blocked in each animal studied, 0.2 mL of vehicle or RTX (0.2 or 2 μg) was given close to each intercostal nerve.

Statistical Analysis

Data are presented as mean \pm SEM. Behavioral analysis comparisons were performed at each time point with the Kruskal-Wallis test followed by the Dunn test. The incidence of nocifensive behavior

among groups was compared by the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

The withdrawal threshold was 15.1 ± 0.14 g in animals before the experiments. Fifty animals underwent thoracotomy, and 21 of 50 (42%) showed a change in withdrawal threshold that started to decrease 10 days after injury and was significantly decreased by 3 wk after thoracotomy (0.45 ± 0.15 g; $P < 0.05$). After the day of injection (Day 10), RTX at doses of 0.8 and 8 μg failed to increase or decrease withdrawal threshold in injured animals at any time point throughout the study (Fig. 1). Uninjured animals that received RTX showed a significant transient decrease in withdrawal threshold compared with vehicle-injected animals (Fig. 2) ($P < 0.05$).

Of note, no signs of sedation, difference in grooming patterns, or exploratory behavior were observed at any time during the experiment.

DISCUSSION

This study suggests that intercostal RTX does not reduce the allodynia after experimental thoracotomy and causes a transient allodynic response in uninjured animals. In this study, nearly 50% of rats developed allodynia after thoracotomy, a result that replicates the findings of Buvanendran et al.¹⁰ In the original model, cold and mechanical allodynia showed a similar timing. In contrast to the original published rib retraction model in which the authors also evaluated cold allodynia, we tested only mechanical allodynia because clinical evidence suggests that the most common reported symptoms in humans after thoracotomy are spontaneous and mechanical evoked pain.²⁻⁴ In the postthoracotomy pain animal model, intrathecal morphine, clonidine, gabapentin, and neostigmine were able to reduce the allodynia even when they were injected after chronic pain was already established. Given that TRPV-1 is peripheral, once chronic pain was established, we knew that proving RTX effective for treating mechanical allodynia would have been difficult to accomplish. However, we had some evidence from the literature that peripherally administered capsaicin has been effective in decreasing the allodynia in some humans affected by postherpetic neuralgia.¹⁸ We also know from our previous study of the postthoracotomy animal model that peripherally injected bupivacaine is effective for improving allodynia once chronic pain has been established.¹⁹ We expected that injured intercostal afferents and inflammatory mediators would have sensitized TRPV-1 receptors on C-unmyelinated¹⁰ and A-myelinated²⁰ fibers.

Failure to improve allodynia after thoracotomy might be due to the fact that the intercostal route allows a significant systemic absorption of the drug administered,^{21,22} leaving the intercostal nerve with a relatively low amount of drug available at the peripheral effector site. The initial amount of drug close to the intercostal nerve would be consistently high to excite the TRPV-1 receptors as shown in uninjured animals (Fig. 2). Evidently, the same amount of drug may not be present for enough time in the nerve surroundings because of a quick systemic absorption that might limit the antiallodynic actions of RTX necessary for supporting its therapeutic use after intercostal nerve injury. In fact, when systemic absorption occurs, RTX fails to reverse tactile allodynia in rats with injury to central nerves.²³ If so, the intrathecal and epidural routes might offer the advantage of less systemic absorption than the intercostal injections along with a potential advantage of decreasing the dose used. It would be worth determining in a future study whether the neuraxial route is effective in relieving mechanical allodynia after thoracotomy in

rats, which might have practical implications in clinical settings where the combined use of intraoperative and postoperative epidural analgesia has been shown to dramatically decrease the incidence of pain at 6 mo after thoracotomy.⁸ Xu et al.¹⁵ found that large doses of systemic RTX (0.5 mg/kg) cause a transient mechanical hypoalgesic response in uninjured rats. RTX might alter the perception of mechanical stimuli, exerting its mechanism of action by activating a supraspinal circuit. These results, along with the evidence that intrathecal RTX produces a prolonged antinociceptive response in a canine model of bone cancer pain,²⁴ suggest a dual mechanism of action that RTX exerts on spinal and supraspinal neuronal circuits depending on the dose and the site of administration. Even if we assume that most of the dose used in this study was absorbed systemically, the amount given is approximately 60–600 times lower than what was given systemically by Xu et al. to appreciate a significant hypoalgesic effect on the mechanical response to von Frey hair testing. This might be another reason why we saw no hypoalgesic response after RTX intercostal injections.

A limitation of this study is that a group of animals that underwent RTX administration before nerve injury was not in the design of the current research project, and hence, no conclusions can be obtained regarding the effectiveness of RTX as a preemptive analgesic drug in the postthoracotomy pain model. In support of our findings, Kissin et al.²⁵ injected RTX in animals that developed mechanical allodynia after loose ligation of the sciatic nerve, and the effect was minimal on mechanical allodynia. In the same study, they found that perineural RTX administered before surgery completely prevented a ligation-induced reduction in withdrawal latency, increase in paw lift duration, and increase in withdrawal frequency to von Frey filaments. As pointed out by the authors, the TRPV-1 receptors may be more important for the induction of hyperalgesia than for its maintenance.

We therefore do not know whether the timing of RTX administration is critical in the postthoracotomy animal model (something that is important to find out in future studies) because preemptive thoracic epidural analgesia in humans reduces long-term pain after thoracotomy.⁸

Another limitation of this study is that we could test the animals only for mechanical allodynia (von Frey hair) and not for mechanical hyperalgesia because other devices, such as the Analgesy-Meter, would have been impractical or difficult to use in the rat's thoracic area. In addition, studies have shown that RTX administration is associated with a reduction in mechanical hyperalgesia tested by the Analgesy-Meter device applied at the hindpaws.¹⁶ Thus, it remains unclear whether RTX reduces mechanical hyperalgesia after intercostal nerve injury.

We also do not know whether higher doses of intercostal RTX would have been effective in reducing

the mechanical allodynia after thoracotomy. Because different doses of RTX have been used for the treatment of experimental pain conditions and because intercostal RTX has not been reported in the literature, we chose our dose based on previous reports^{26–28} and on a pilot study conducted in our laboratory evaluating the spontaneous hyperalgesic response after RTX administration.

In contrast to a recent preclinical study showing that after RTX injection animals did not display nociceptive behaviors,²⁷ our results show that the initial allodynic response follows RTX administration and is more evident in uninjured than injured animals. We think that the difference was difficult to show in injured animals because the withdrawal threshold force was significantly low once the allodynia was established and before RTX injection. These results suggest that it would be advisable to administer RTX along with local anesthetics to prevent or attenuate the initial hyperalgesic response.

Because no sign of sedation, difference in grooming pattern, or exploratory behavior was observed in the animals at any time during the experiment, the likelihood of systemic toxicity in our study is minimal.

In conclusion, the current results strongly suggest that no single model is adequate to investigate the possible mechanisms that underlie neuropathic pain. The next step in discovering whether RTX has clinical applications for the prevention and treatment of neuropathic pain that follows intercostal nerve injury is to consider other options of drug administration such as the intrathecal or the epidural route and different timing of RTX injection before or during nerve injury.

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CME Magnetic Resonance Imaging Findings After Uneventful Continuous Infusion Neuraxial Analgesia: A Prospective Study to Determine Whether Epidural Infusion Produces Pathologic Magnetic Resonance Imaging Findings

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BACKGROUND: Magnetic resonance imaging (MRI) is considered the preferred diagnostic tool to determine whether postepidural neurologic symptoms are due to hematoma or abscess. However, there is currently no published information regarding the normal appearance of a MRI after a continuous epidural infusion. In this prospective cohort study, we defined the characteristic appearance of MRI findings after uneventful epidural analgesia.

METHODS: Thirty women were prospectively enrolled to undergo a lumbar MRI after labor and delivery. The study group consisted of 15 women who received neuraxial analgesia with a combined spinal epidural technique followed by continuous epidural infusion, whereas the control group included 15 women who delivered without receiving neuraxial analgesia. All patients received a MRI within 12 h of delivery via a 1.5T scanner. MRIs were reviewed by two neuroradiologists who were blinded to the patient's study group allocation and asked to document the presence or absence of fluid collection, air collection, or soft tissue abnormalities.

RESULTS: There were no radiologically significant fluid collections, hematomas, or mass effects noted on the thecal sac of any of the 30 MRI studies. A small amount of epidural air was seen in 77% of MRI studies after epidural analgesia, but there was no indentation on the thecal sac.

CONCLUSIONS: The lack of significant collections or mass effects seen in the MRIs of our patients after continuous infusion of epidural analgesia suggests that the presence of these findings in a patient with new neurologic symptoms after administration of epidural analgesia should be considered pathologic and warrant immediate attention.

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Epidural and spinal infection, hematoma, and nerve injury are rare complications of central neuraxial blockade (CNB). Several large retrospective studies have estimated that these complications occur in the range of 1/100,000.¹⁻³ Recent reports, however, have suggested a much higher incidence.⁴⁻⁷ Confirmation of the diagnosis in a patient with new onset of

neurologic symptoms after a CNB is a relative emergency, because neurological prognosis worsens as the delay increases between the spinal insult and treatment, such as decompressive laminectomy or antibiotic therapy.^{8,9}

In recent years, there has been a dramatic increase in the availability and use of magnetic resonance imaging (MRI),⁵ which is the preferred diagnostic tool applied to the clinical situation when there is a possibility of hematoma, abscess, or injury after CNB.¹⁰⁻¹² However, one factor that may contribute to some uncertainty regarding the use of MRI for diagnosis in these situations is the lack of scientific documentation of normal MRI findings after uneventful epidural infusions. Radiologists may experience difficulties with interpretation of MR scans after epidural injections and continuous infusions in parturients. For instance, it has been suggested that engorgement of the epidural venous plexus in pregnant woman,¹³ epidural injections,¹⁴ unintended epidural vein puncture, and cerebrospinal fluid (CSF) leak after dural puncture¹⁵ may all produce signal distortion on an MRI scan. Furthermore, other benign situations seen

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in this group of patients, such as epidural catheter placement, have also been reported to produce MRI changes that may mimic spinal pathology.^{16–18}

MRI of patients with uneventful epidural injections may serve as a baseline for comparison. We have recently evaluated MRI findings after an uneventful single epidural injection in chronic pain patients¹⁹ and did not find any cases of indentation of the thecal sac.

The purpose of this prospective cohort study was to compare MRIs of parturients shortly after giving birth with or without epidural analgesia to define the characteristic appearance of MRI findings in healthy parturients after uneventful epidural labor analgesia.

METHODS

Study Population

After IRB approval and signed informed consent, 30 parturients were prospectively enrolled to undergo a lumbar MRI after delivery. The study group consisted of 15 women who received combined spinal epidural (CSE) analgesia. The control group included 15 women who delivered without receiving neuraxial analgesia. All 30 parturients received an MRI of the lumbar spine within 3–12 h of labor and delivery. All patients who received neuraxial analgesia had the epidural catheter removed before performance of the MRI. No patients had a history of spine surgery or other conditions that would impact the MRI results, and no patients received nitrous oxide in labor.

CSE Technique

Each CSE injection was performed with the patient in the sitting position using the needle-through-needle technique. A 17-G Tuohy needle (B. Braun, Bethlehem, PA) was placed via the midline approach using loss-of-resistance (LOR) to air technique while injecting a maximum of 2 mL of air. More than one pass during placement of the epidural needle was permissible, as long as there was no bloody return. After identification of the epidural space, a 26-G 12.4-cm atraumatic spinal needle (Arrow International, Reading, PA) was inserted into the subarachnoid space and the location verified by appearance of CSF in the needle hub. On subarachnoid placement, 20- μ g fentanyl was injected after which the spinal needle was withdrawn. The epidural needle was flushed with 10 mL of preservative-free normal saline before advancing the epidural catheter 5 cm. An epidural infusion of bupivacaine 0.1% with 3- μ g/mL fentanyl was then administered at 10–14 mL/h. No epidural test dose was given.

Parturients who did not achieve adequate analgesia or who did not receive at least 2 h of epidural infusion before delivery were excluded. In addition, any patient who experienced a “bloody tap” or unanticipated dural puncture (“wet tap”) was also excluded.

Magnetic Resonance Imaging

All patients received MRI within 3–12 h of delivery. Spinal MRI of the lumbar region was performed on a

1.5T scanner using a spine surface coil. Sagittal images were acquired with the following sequences: T2-weighted fast spin echo images; T1-weighted spin echo images; T2 gradient echo images; T2 STIR images. Axial images were acquired with the following sequences: T2-weighted fast spin echo images; T1-weighted spin echo images; T2 gradient echo images; T2 fat-saturated images. Gadolinium, which is sometimes used clinically, is not necessary to identify a fluid collection and was not used because of a potential interference with breastfeeding.²⁰

MRI Evaluation

Data Analysis

The MRI were reviewed by two neuroradiologists who were blinded as to whether the images that they were viewing were from the study group (CSE) or from the control group (no CSE). Each of the radiologists independently evaluated the MRI scans and documented the presence or absence of epidural or paravertebral abnormalities, including the presence of fluid collection, air collection, or soft tissue abnormalities. They were specifically asked to note the presence of an air or a fluid collection. If a collection was present, its dimensions were documented and any mass effect exerted on the dural sac. The neuroradiologists were also asked to determine if a needle track could be identified and to predict if a CSE technique preceded the MRI study being evaluated.

Statistical Analysis

Data were reported as means \pm standard error or percent and standard error. Reported test data were pooled over neuroradiologist readers. *t*-test was used to compare the demographic and labor data between the two groups. A generalized linear model analysis with generalized estimating equations technique was used to compare MRI findings between the CSE and control groups.^{21,22} No *P* value is reported for analyses, where there were no findings for one or both readers. Statistical tests with results having probabilities of 0.05 or less were considered statistically significant. SAS 9.1 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

There were no significant differences between the control and CSE groups in demographics (Table 1). No epidural was in place for more than 12 h. None of the patients receiving neuraxial blockade had an unanticipated dural puncture (wet tap) with the epidural needle and there were no postepidural complications. There were no significant fluid collections, hematomas, or mass effects noted on the thecal sac in any of the 30 MRI studies (Table 2). A small amount of epidural air (<10 mm) was seen in 77% of MRI studies after epidural block (Figs. 1 A and B). The largest collection of epidural air measured 8 mm \times 6 mm in its widest diameter with no indentation on the thecal

Table 1. Demographic and Labor Data for the Control and CSE Groups

| Patient characteristics | Control ^a (n = 15) | CSE ^a (n = 15) | P |
|---------------------------|----------------------------------|------------------------------|-------|
| Age (yr) | 25.4 ± 1.4 | 24.9 ± 1.4 | 0.788 |
| Weight (kg) | 77.0 ± 3.2 | 78.5 ± 4.7 | 0.787 |
| Height (m) | 1.6 ± 0.02 | 1.6 ± 0.01 | 0.479 |
| BMI (kg/m ²) | 29.2 ± 1.1 | 29.2 ± 1.7 | 0.986 |
| Time to MRI (h) | 10.2 ± 0.7 | 8.7 ± 0.9 | 0.227 |
| Total volume infused (mL) | NA | 80.7 ± 12.0 | |

^aMean ± SE.

CSE = combined spinal epidural; MRI = magnetic resonance imaging; BMI = body mass index.

Table 2. Magnetic Resonance Imaging (MRI) Findings

| MRI findings | CSE ^a |
|------------------------------|------------------|
| Thecal compression | 0 |
| Epidural air | 76.7 ± 7.7 |
| Epidural fluid collection | 3.3 ± 3.3 |
| Paravertebral edema | 43.3 ± 9.0 |
| Needle track | 50.0 ± 9.1 |
| Correct group identification | 93.3 ± 6.2 |

^aPercent ± SE.

CSE = combined spinal epidural.

sac. An injection track was identified in 50% of the 15 studies that were performed after neuraxial injections (Figs. 2 A and B).

Abnormal signal intensity in the paraspinal musculature was seen in 43% of MRI studies after epidural block (Fig. 3). These ill-defined soft-tissue abnormalities demonstrated low signal intensity on the gradient-echo images and high signal intensity on the T2 fat-saturated images, the largest of which measured 3.0 × 4 cm in maximum dimensions. The image readers were able to correctly distinguish if a neuraxial technique preceded the MRI study in 93% of the cases.

DISCUSSION

The occurrence of a hematoma or an abscess after neuraxial block is an extremely uncommon event, but one that may be associated with permanent neurologic dysfunction. Confirmation of spinal hematoma or infection is considered to be an emergency because neurological prognosis depends on the time between occurrence of neurological symptoms and performance of decompressive laminectomy.^{8,9}

When evaluating the postpartum patient with neurologic symptoms after neuraxial blockade, clinicians cannot rely on clinical signs alone and radiologic assessment may become necessary. Royackers et al.²³ advocated MRI scans in any patient after epidural injection who develops back pain and any evidence of local or systemic infection, whereas others suggest more selective criteria.⁵

The need for postpartum radiologic evaluation of new or progressive neurologic deficits is not insignificant. In

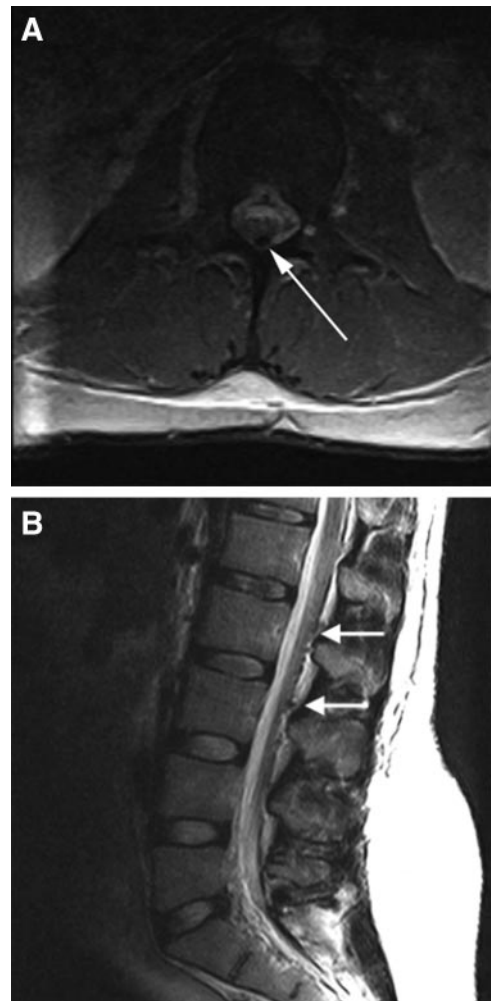


Figure 1. Gradient echo axial (A) and sagittal (B) images. Arrow shows air in the epidural space without mass effect on the dural sac.

a prospective study, Viitanen et al.²¹ investigated the incidence of postpartum neurologic symptoms after spinal blockade for labor analgesia. Thirty seven percent of parturients complained of various neurological symptoms during the first week after delivery, including headache (27%), new onset back pain (13%), and transient neurologic symptoms (4%). Others have reported even higher rates of postpartum back pain.²² Although most postpartum neurologic symptoms are due to obstetric factors, MRI is useful to exclude other causes. Furthermore, a study by Grewal et al.²⁴ reported that the “classic” clinical triad for spinal abscess (back pain, fever, and neurological deficit) occurred in only 13% of patients by the time they were first evaluated.

Despite the fact that MRI studies are advocated as the first line of diagnostic evaluation in patients with the new onset of lower extremity weakness after neuraxial block, it has been suggested that the MRI results may be confusing or uninterpretable after a neuraxial blockade.^{17,18} Ikushima et al.¹⁶ studied five patients who were treated with epidural infusions and reported false pathologic findings that mimic those of

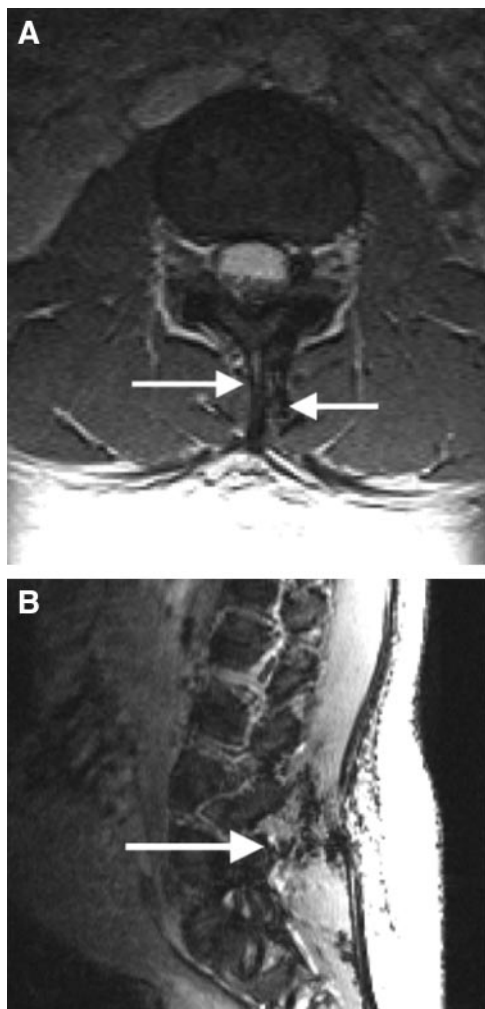


Figure 2. Gradient echo axial (A) and sagittal (B) images. Arrow shows needle track in the posterior paraspinal soft tissues of the back.

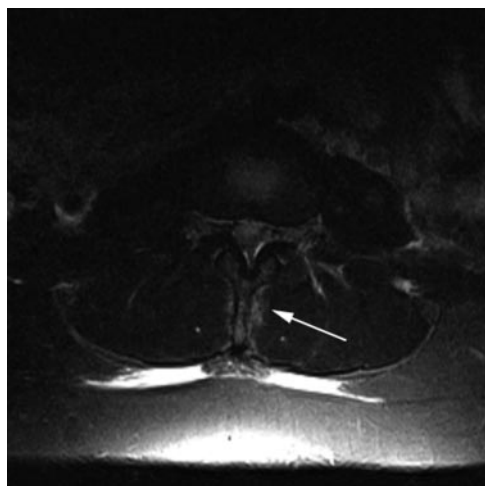


Figure 3. Abnormal signal intensity in the paraspinal musculature. Axial T2 with fat saturation technique shows high signal in the same area suggestive of edema.

epidural abscess in the absence of infection in MRI studies. The lesions were located in the posterior epidural space at the site of catheter insertion. All lesions

were hypointense relative to the spinal cord on T1-weighted images and isointense to CSF on T2-weighted images reflective of the highly vascularized and increased water content of the inflammatory cells. The false-positive findings of Ikushima et al., in contrast to ours, raise the possibility that the duration of time of the indwelling epidural catheter (up to 25 days in the study of Ikushima et al.) may account for this difference.

In this study, a continuous epidural infusion of 10–14 mL/h (average total of 80 mL of epidural infusion) was administered. These volumes are commonly administered for postoperative pain management and for labor analgesia. Based on previous reports, these epidural infusions might produce a mass effect appearance similar to that observed after epidural blood patch. Dural sac compression by epidurally injected solutions has been reported.²⁵ Higuchi et al.¹⁴ demonstrated that 5–15 mL of epidurally administered saline produced dural compression that was gradually restored. Several studies have described MRI findings after epidural blood patch. Griffiths et al.²⁶ and Vakharia et al.²⁷ have demonstrated that an epidural blood patch produces considerable mass effect with significant compression of the thecal sac and exiting nerve roots.²⁷ These thecal compression findings were dynamic and were found to be present at 30 min and 3 h.²⁸ After 18 h, only small scattered clots remained adherent to the thecal sac. In our study, we did not follow the postepidural MRI findings at different times, but the times chosen were clinically significant, as these would most likely be the times that neurologic assessment would be needed in a case with postpartum neurologic symptoms. As compared with the epidural blood patch studies, we found that no mass effect was observed. This raises the possibility, however, that the delay until performance of the MRI allowed any temporary pressure changes to diminish.

As in our previous study,¹⁹ we observed that epidural air and needle tracks are common findings after uneventful epidural injections. Although we limited the volume of air in our protocol to 2 mL, the radiologists were still able to detect air in 75% of the MRIs after epidural placement. Of note, these findings did not produce any significant mass effect on the dural sac, and thus, would not have warranted medical intervention. Dalens et al.²⁹ also reported that it is not uncommon to view epidural air after neuraxial anesthesia. Garcia et al.³⁰ described air in the epidural space after epidural anesthesia with LOR to saline. They concluded that air may be entrapped through the tissues along the needle track and does not have to be administered via the LOR to air technique. Our study demonstrates that air in the epidural space after epidural injection is commonly seen and should not be regarded as a pathological finding and does not preclude the radiologist from correctly interpreting the MRI.

A potential shortcoming of this study may be the small number of patients observed. When dealing with rare complications, such as severe neurological complications after neuraxial blockade, large studies including more than 100,000 have been used.^{2,3} The purpose of our study was not to evaluate neurologic dysfunction, but rather to provide a "reference" for normal MRI findings after routine epidural infusion. This documentation, which is necessary for radiologists who are being asked to interpret MRI scans after epidural infusions, is important preliminary information. Further larger studies are warranted to get a more complete understanding of normal MRI results in other situations, such as after postoperative epidural analgesia with catheters remaining *in situ* for longer periods or other patient populations.

In conclusion, MRI findings after a continuous infusion of epidural analgesia in this preliminary study were not pathological. The lack of significant collections or mass effects seen in our patients suggests that the presence of these findings in a postpartum patient with new neurologic symptoms should be considered pathologic and warrant immediate attention.

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The Systemic Toxicity of Equipotent Proxymetacaine, Oxybuprocaine, and Bupivacaine During Continuous Intravenous Infusion in Rats

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BACKGROUND: Although proxymetacaine and oxybuprocaine produce topical ocular and spinal anesthesia, they have never been tested as cutaneous anesthetics. We compared cutaneous analgesia of proxymetacaine and oxybuprocaine with bupivacaine and tested their central nervous system and cardiovascular toxicity.

METHODS: After blockade of cutaneous trunci muscle reflex with subcutaneous injections, we evaluated the local anesthetic effect of proxymetacaine and oxybuprocaine on cutaneous analgesia in rats. After IV infusions of equipotent doses of oxybuprocaine, proxymetacaine, and bupivacaine, we observed the onset time of seizure, apnea, and impending death and monitored mean arterial blood pressure and heart rate.

RESULTS: Proxymetacaine and oxybuprocaine acted like bupivacaine and produced dose-related cutaneous analgesia. On a 50% effective dose basis, the ranks of potencies were proxymetacaine > oxybuprocaine > bupivacaine ($P < 0.01$). Under equipotent doses, the infusion times of proxymetacaine or oxybuprocaine required to cause seizure, apnea, and impending death were longer than that of bupivacaine ($P < 0.05$). The decrease in mean arterial blood pressure and heart rate was slower with oxybuprocaine and proxymetacaine compared with bupivacaine ($P < 0.05$ for the differences) at equipotent doses.

CONCLUSIONS: Oxybuprocaine and proxymetacaine were more potent at producing cutaneous anesthesia but were less potent than bupivacaine at producing central nervous system and cardiovascular toxicity.

(Anesth Analg 2010;110:238-42)

Topical ocular anesthesia has been part of ophthalmology for more than a century.¹ The most frequently used drugs include proparacaine (proxymetacaine), benoxinate (oxybuprocaine), tetracaine, lidocaine, and bupivacaine. Oxybuprocaine and proxymetacaine (Fig. 1), 2 ester anesthetics, are frequently used drugs for topical ocular anesthesia because of the ease of administration and minimal side effects.¹ Clinically, ocular anesthesia is performed with topical 0.5% proxymetacaine for patients undergoing strabismus

surgery and posterior vitrectomy^{2,3} and with topical 0.4% oxybuprocaine for penetrating trabeculectomy, repair of a ruptured globe, and cataract surgery.⁴⁻⁶ Many publications have reported the successful treatment of trigeminal neuralgia by topical anesthetic oxybuprocaine or proxymetacaine instilled in the eye of the affected side.^{4,5}

Injection of local anesthetics into tissues is a recommended method for postoperative pain control and surgical anesthesia because it produces relatively few side effects.⁷ However, the technique is limited by the short duration of analgesia or anesthesia.⁸ For this reason, bupivacaine is chosen for infiltration because of its longer duration of effective analgesia.⁹ Recently, we showed that oxybuprocaine and proxymetacaine were more potent at producing spinal anesthesia in rats, when compared with bupivacaine or lidocaine.¹⁰ Oxybuprocaine and bupivacaine produced similar durations of spinal blockade and a more sensory-selective action over motor blockade.¹⁰ However, cutaneous analgesia after infiltration of oxybuprocaine and proxymetacaine has not been evaluated. In this study, we compared infiltration anesthesia of oxybuprocaine and proxymetacaine with bupivacaine. We also evaluated the systemic toxicity of the 3 drugs by infusing equipotent doses of the drugs.

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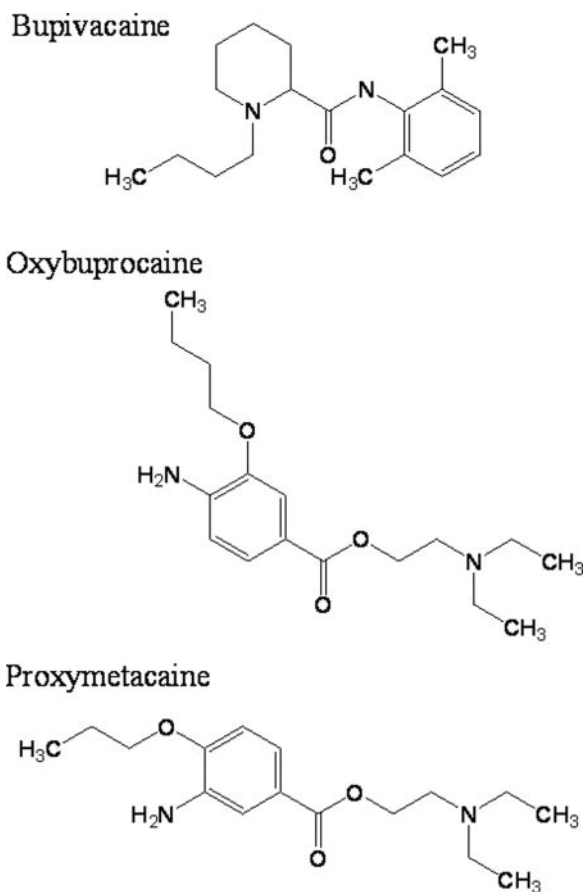


Figure 1. The chemical structures of bupivacaine, oxybuprocaine, and proxymetacaine.

METHODS

Animals

Male Sprague-Dawley rats weighing 275–325 g were obtained from the National Laboratory Animal Centre, Taipei, Taiwan. Sixty-four rats were housed in groups of 3, with food and water freely available until the time of testing. The climate-controlled room was maintained at 24°C with approximately 50% humidity and a 12-h light/dark cycle (6:00 AM to 6:00 PM). The experimental protocols were approved by the Animal Investigation Committee of China Medical University, Taichung, Taiwan and conformed to the recommendations and policies of the International Association for the Study of Pain.

Drugs

Proxymetacaine HCl (proparacaine HCl), oxybuprocaine HCl (benoxinate HCl), and bupivacaine HCl were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). All drugs were freshly prepared in normal saline (0.9% NaCl) before the subcutaneous injections or IV infusion.

Infiltrative Cutaneous Analgesia

Before subcutaneous injections, the hair on the rats' dorsal surface of the thoracolumbar region (10 × 10 cm²) was mechanically removed. Each drug was injected into a naïve area of the rat's shaved back. The

back was divided into 4 quadrants (to clearly demarcate injection and control sites), and each rat received each study drug. Each animal was injected twice with the drug being tested and separated by an interval not <5 days. Subcutaneous injections of drugs were performed as reported previously.¹¹ Briefly, 0.6 mL of the drugs was injected subcutaneously at the dorsal surface of the thoracolumbar region of the unanesthetized rats. After subcutaneous injection, the wheal was marked with ink within 30 s after injection. A von Frey (No. 15, Somedic Sales AB, Stockholm, Sweden) filament (19 g), to which the cut end of an 18-gauge needle was affixed, was used to standardize the stimulus intensity on the rat's skin. Six pinpricks (at 6 different points within each wheal) with a frequency of 0.5–1 Hz were used in each testing. Each drug's cutaneous anesthetic effect was evaluated quantitatively as the number of times the pinprick failed to elicit a response of cutaneous trunci muscle reflex. For example, the complete absence of 6 responses was defined as complete block (100% of possible effect [PE]). During the test, the maximum value of %PE was presented as percent of maximal PE (%MPE). Each drug's duration of action was defined as the time from drug injection (i.e., time = 0) to full recovery of cutaneous trunci muscle reflex (no analgesic effect was found or 0% of MPE recorded).¹¹

After subcutaneously injecting the rats with different doses of each drug ($n = 8$ for each dose of each drug), dose-response curves were constructed using the %MPE for each dose of each drug. The curves were then fitted using a computer-derived SAS NLIN analysis (SAS Institute, Cary, NC, version 9.1; SPSS for Windows, version 12.0), and the values of 50% effective dose (ED₅₀), defined as the doses that caused 50% cutaneous analgesia, were obtained.^{12,13} Drug potencies were compared with dose responses. Durations of drug effect defined as the intervals from injection to complete recovery were measured.

Measurements of Systemic Toxicity and Hemodynamic Variables

Animals were anesthetized with an intraperitoneal injection of pentobarbital sodium (45 mg/kg), and the right femoral artery and vein were cannulated with polyethylene catheters (PE-50), which were filled with heparin saline (30 U/mL). The free end of the catheter was threaded through an 18-gauge needle and then tunneled subcutaneously. The catheter was cut with 5 cm protruding from the skin at the midline in the posterior cervical area and sealed by heating it with a match and compressing it with a hemostat.¹⁴

On Day 2, the animals were placed in a small cage with an open top to allow the lines to reach the animal and prevent the animal from chewing on the lines. The tube in the femoral artery was connected to a transducer, and mean arterial blood pressure (MAP) and

Table 1. Baseline Data are Shown as Mean \pm SEM

| Variable | Saline | Bupivacaine | Proxymetacaine | Oxybuprocaine |
|-------------|--------------|--------------|----------------|---------------|
| Body weight | 302 \pm 18 | 298 \pm 8 | 311 \pm 10 | 307 \pm 10 |
| MAP | 107 \pm 3 | 105 \pm 3 | 103 \pm 3 | 105 \pm 1 |
| HR | 419 \pm 12 | 400 \pm 13 | 438 \pm 15 | 413 \pm 19 |

There were no significant differences among the groups for these variables.

MAP = mean arterial blood pressure; HR = heart rate.

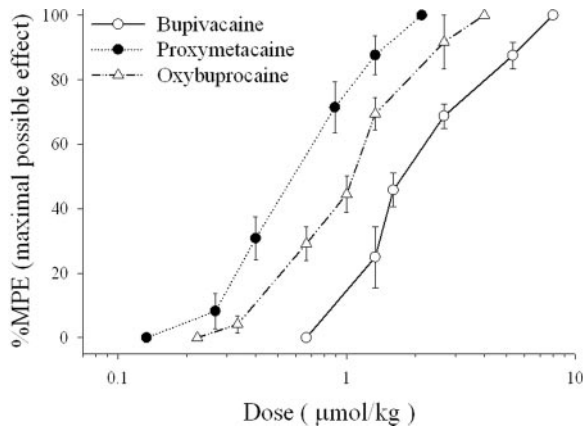


Figure 2. The dose-response curves of proxymetacaine, oxybuprocaine, and bupivacaine on infiltrative cutaneous analgesia in rats ($n = 8$ at each testing point). Data are presented as mean \pm SEM.

Table 2. The 50% Effective Doses (ED_{50} s) of Drugs

| Drug | ED_{50} s (95% CI) |
|----------------|----------------------|
| Bupivacaine | 1.89 (1.68–2.12) |
| Proxymetacaine | 0.59 (0.52–0.68) |
| Oxybuprocaine | 1.01 (0.93–1.09) |

ED_{50} s of drugs ($\mu\text{mol/kg}$) were obtained from Figure 2.

Potencies of drugs (ED_{50} s) were proxymetacaine > oxybuprocaine > bupivacaine ($P < 0.01$, for each comparison) using a 1-way analysis of variance followed by pairwise Tukey's honestly significant difference test.

CI = confidence interval.

heart rate (HR) were recorded using a polygraph (MP36, BIOPAC Systems, Goleta, CA). The tube in the right femoral vein was connected to an infusion pump (Harvard Model 22 Infusion Pump, Harvard Apparatus, Holliston, MA) for delivery of the drugs.¹⁵ The investigator (C-HH) was blinded to the drugs under study. After IV infusions of either 1) bupivacaine at $8.00 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, proxymetacaine at $3.56 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, or oxybuprocaine at $6.67 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or 2) normal saline ($n = 7$) at a rate of $400 \mu\text{L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the onset time of seizure, respiratory arrest, time to cause impending death, MAP, and HR were evaluated. Rats were evaluated 2 min before infusion medication and at 5-min intervals to 105 min.

The onset time of seizure was defined as the time when the first convulsion occurred¹⁴ and respiratory arrest when apnea occurred for 15 s by observation of chest movement. The time to impending death was defined as the time it took for the HR to decrease to 0 per minute.

Statistical Analysis

Values are presented as mean \pm SEM or ED_{50} values with 95% confidence interval. The differences in ED_{50} values among drugs were evaluated by a 1-way analysis of variance (ANOVA) followed by pairwise Tukey's honestly significant difference test. The differences in baseline data and the time to cause toxicity between medications were evaluated using 1-way ANOVA and then the pairwise Tukey's honestly significant difference test. ANOVA with repeated measures followed by Duncan's multiple-range test was used for *post hoc* multiple comparisons of means on MAP and HR. SPSS for Windows (version 12.0) was used for all statistical analyses. Statistical significance was set at $P < 0.05$.

RESULTS

The baseline data of body weight, MAP, and HR showed no significant differences among groups (Table 1). Proxymetacaine, oxybuprocaine, and bupivacaine produced dose-dependent infiltration anesthesia in rats (Fig. 2). The ED_{50} values of drugs are shown in Table 2. For ED_{50} , the relative potency of these drugs was found to be proxymetacaine > oxybuprocaine > bupivacaine (Table 2). All rats recovered completely after each subcutaneous injection. At dosages of $8.00 \mu\text{mol/kg}$ for bupivacaine, $3.56 \mu\text{mol/kg}$ for proxymetacaine, and $6.67 \mu\text{mol/kg}$ for oxybuprocaine, all the local anesthetic drugs caused 100% blockade with durations of actions of 110 ± 11 , 93 ± 9 , and 128 ± 8 min, respectively (Figs. 2 and 3). Saline produced no infiltration anesthetic effects.

At equipotent doses, the times required to cause seizure, respiratory arrest, and impending death were longer in the oxybuprocaine group than in the bupivacaine or proxymetacaine group (Fig. 4). MAP and HR showed a tendency to decrease before cardiovascular (CV) collapse (Fig. 5) in all study groups. The decreases in MAP and HR were slower in the proxymetacaine or oxybuprocaine groups compared with the bupivacaine group (Fig. 5). The rapidity of decrease of MAP and HR occurred in the following order: bupivacaine > proxymetacaine > oxybuprocaine (Fig. 5).

DISCUSSION

Our study showed that proxymetacaine, oxybuprocaine, and bupivacaine produced dose-dependent infiltration anesthesia. At equipotent doses, systemic toxicity after IV proxymetacaine or oxybuprocaine occurred later compared with bupivacaine.

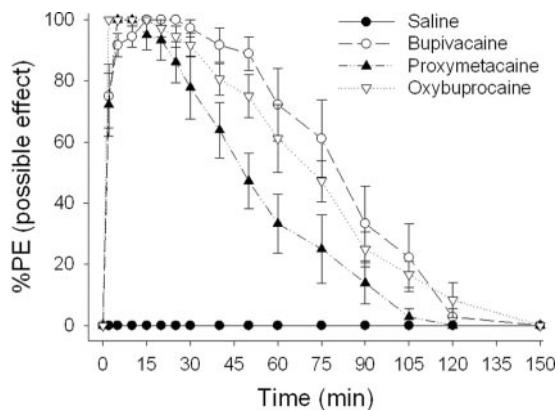


Figure 3. Time courses of infiltrative cutaneous analgesia of proxymetacaine at $3.56 \mu\text{mol}/\text{kg}$, oxybuprocaine at $6.67 \mu\text{mol}/\text{kg}$, and bupivacaine at $8.00 \mu\text{mol}/\text{kg}$ in rats. Data are presented as mean \pm SEM; each group, $n = 8$.

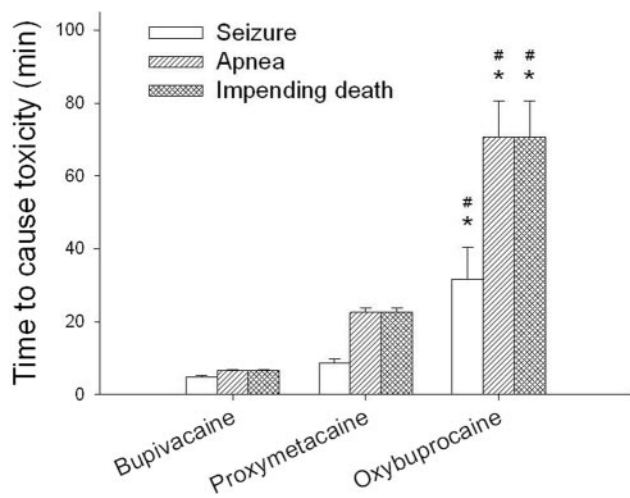


Figure 4. Time to cause toxicity (at equipotent doses) of bupivacaine, proxymetacaine, and oxybuprocaine at the onset of seizure, respiratory arrest, and time to cause impending death. Toxicity symptoms were not detected in the saline group ($n = 7$) (data not shown). Symbols (*) indicate $P < 0.05$ for proxymetacaine or oxybuprocaine compared with bupivacaine. Data are presented as mean \pm SEM.

Infiltrative cutaneous anesthesia is an attractive option for management of postoperative pain and surgical anesthesia because it is relatively free of side effects.¹⁶ In this study, proxymetacaine and oxybuprocaine were found to have a local anesthetic effect that was more potent than bupivacaine, a long-acting local anesthetic. Recently, we showed that intrathecal injections of oxybuprocaine, proxymetacaine, bupivacaine, and lidocaine produced dose-related spinal anesthesia.¹⁰ Proxymetacaine and oxybuprocaine produced almost 4.1- and 2.4-fold greater potency, respectively, than did bupivacaine, when used as a spinal anesthetic in rats.¹⁰ Based on dose-response curves, proxymetacaine and oxybuprocaine were more potent than bupivacaine.¹⁰ There seems to be a uniformity of the comparative potencies of proxymetacaine, oxybuprocaine, and bupivacaine with respect to cutaneous analgesia and spinal anesthesia.

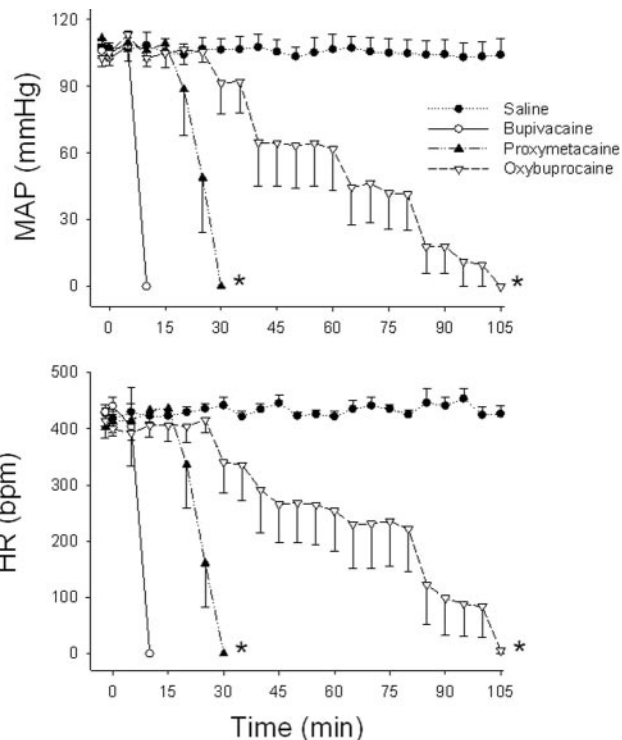


Figure 5. Mean arterial blood pressure (MAP) and heart rate (HR) change during infusion of either 1) bupivacaine ($n = 8$) at $8.00 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, proxymetacaine ($n = 8$) at $3.56 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, or oxybuprocaine ($n = 8$) at $6.67 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or 2) normal saline ($n = 7$) in the volume of $400 \mu\text{L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (the same volume given to the animals in the drug group) as infusion; 0 min is the start of infusion. Infusion was stopped when the time to cause impending death was reached. Symbols (*) indicate $P < 0.05$ for proxymetacaine or oxybuprocaine compared with bupivacaine. Data are presented as mean \pm SEM.

Accidental IV injection of local anesthetic may induce central nervous system and CV system toxicity and even cause death.¹⁴ In this study, oxybuprocaine was less potent at producing toxicity compared with bupivacaine or proxymetacaine. However, the degrees of toxicities were the same once toxicity occurred (Fig. 4). We also noted that the decreases in MAP and HR were longer with oxybuprocaine and proxymetacaine compared with bupivacaine. Overall, these results suggest that oxybuprocaine and proxymetacaine are less toxic and better tolerated than bupivacaine after IV injection.

Our study showed that local anesthetic potency does not necessarily mean increased CV toxicity in that proxymetacaine and oxybuprocaine were more potent local anesthetics yet caused less CV toxicity than bupivacaine. It is possible that the 2 drugs are unique local anesthetics. Also, in the previous CV toxicity studies,¹⁷ dogs' lungs were ventilated to maintain their acid-base status and Po_2 at normal levels. However, the role of acidosis and hypoxia is not clear because these occur rapidly after the onset of local anesthetic-induced convulsions in humans.¹⁸ The different results may also have been attributable to species

differences or in the experimental methods. Our results need to be confirmed by other investigators.

In conclusion, our study showed that oxybuprocaine and proxymetacaine are more potent at producing infiltration anesthesia compared with bupivacaine. Intravenous equipotent doses of proxymetacaine or oxybuprocaine produce lower central nervous system and CV system toxicity than bupivacaine. There seems to be a greater margin of safety between the anesthetic dose and the dose that produces toxicity for proxymetacaine or oxybuprocaine compared with bupivacaine. The clinical relevance of these effects warrants further investigation.

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The Use of Regional Anesthesia by Anesthesiologists in Nigeria

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There is growing interest in the use of regional anesthesia worldwide. With this survey, we determined the use of regional techniques among anesthesiologists in Nigeria using a cross-sectional study design. A self-administered questionnaire was mailed to a randomly generated list of anesthesiologists in Nigeria. From 196 questionnaires, 140 anesthesiologists (71.4%) responded. Regular use of spinal, epidural, and peripheral nerve blocks was 92.9%, 15%, and 2.9%, respectively. A high percentage of respondents (47.1%) had never performed a nerve block and only 31.4% had used a nerve stimulator technique. Limited exposure to equipment and techniques accounted for their lack of use.

(Anesth Analg 2010;110:243-4)

Regional anesthesia, particularly peripheral nerve blocks, has become an important anesthetic tool for pain and surgical management during the past century.¹ The use of regional techniques provides site-specific, complete pain relief sufficient for bone and soft tissue operations while avoiding general anesthesia and its attendant risks.² Peripheral blockade facilitates early mobilization and rehabilitation. Placement of a peripheral catheter ensures prolonged analgesia while reducing the need for systemic drugs with their side effects.³ Despite these advantages, the techniques have not been embraced as alternatives to general anesthesia in Nigerian hospitals. In this study, we documented the current practice of regional anesthesia, with a focus on peripheral techniques, among anesthesiologists in Nigeria.

METHODS

We used a cross-sectional study design. The study was based on a completed questionnaire regarding the practice of regional techniques by anesthesiologists in Nigeria. Participants were members of the Nigerian Society of Anesthesiologists with 400 members working in secondary and tertiary hospitals across the country. We estimated the required sample size using the "Stat cal" feature on a population survey⁴ with the following inputs: population size of 400, expected prevalence of use 50%, and a precision of 5%. The

prevalence of 50% gave the optimum sample size required because we do not have prior information on the prevalence of use in our environment. The sample size obtained assuming a type 1 (α) error of 0.05 was 196. Using a table of random figures, a list of 196 anesthesiologists was generated from the Nigerian Society of Anesthesiologists register. A self-administered questionnaire was then mailed to each member in the randomly generated list and followed up 4 wk later with another mailing to nonrespondents. The questionnaire focused on techniques, frequency of use, barrier to use, exposure to peripheral nerve block techniques and equipment during residency training, and perceived roles of peripheral nerve block in their future practice. Responses were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL) version 11.0. Data analysis included frequencies, percentages, and χ^2 statistical test. The chart was generated using Microsoft Excel. A *P* value of <0.05 was considered statistically significant.

RESULTS

One hundred forty anesthesiologists (71.4%) from 196 mailed questionnaires responded. The responders' clinical experience ranged from 1 to 29 yr in practice; of these, 29.3% were senior anesthesiologists (Consultants and Senior Registrars). Among the respondents, 92.9% indicated that they regularly used (i.e., used whenever a surgical procedure is amenable to a regional technique) spinal block in their practice. However, only 15.0% reported regular use of epidural techniques and 25.7% reported that they never performed epidural block. Regular use of peripheral nerve block was reported by only 2.9% and almost half (47.1%) had never attempted a peripheral nerve block. The majority of anesthesiologists in Nigeria reported only occasional use of epidural (59.3%) and peripheral nerve block (50%) techniques.

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Plexus techniques

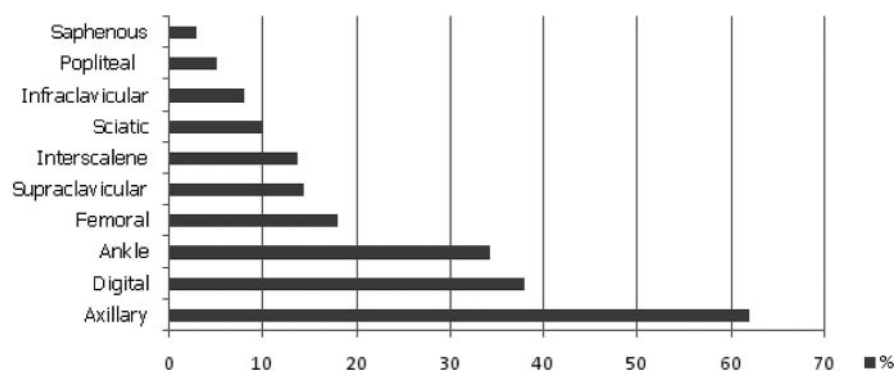


Figure 1. Horizontal bars showing the percentages of anesthesiologists who reported the use of plexus techniques in their practice.

Peripheral nerve blocks of the upper extremity (axillary 62.1%, supraclavicular 14.3%, and interscalene 13.6%) were more frequently used compared with lower limb nerve blocks (ankle 34.3%, femoral 17.9%, sciatic 10%, and popliteal 5%) ($P = 0.0001$) (Fig. 1). Sixty-eight percent believed that the impediment to their use of plexus anesthesia was lack of skill; only 7% admitted they did not have suitable patients.

A majority of anesthesiologists (76.4%) had seen a peripheral nerve stimulator before, but only 31.4% of them used it in their practice. However, a high proportion of anesthesiologists (83.6%) believed that nerve blocks should not be performed without a peripheral nerve stimulator. Most respondents (89%) rated their exposure to peripheral nerve blocks during their residency training as poor and in need of more education with a prediction that their use of regional anesthesia would increase in the future.

DISCUSSION

Our survey showed that despite the potential benefits of regional anesthesia, the techniques are not widely used by anesthesiologists in Nigeria. In a nationwide study conducted in 1995, Hadzic et al.⁵ reported underuse of peripheral nerve blocks in the United States. In this study, we found that upper limb blocks were used frequently, especially the axillary approach to the brachial plexus, compared with lower extremity blocks. This is consistent with findings in the United States.⁵ Regional anesthesia, particularly plexus blocks, are growing in popularity in Europe and the United States, with emphasis on training during the residency program and organized anesthesia societies, such as American Society of Regional Anesthesia, promoting its use.^{6,7} The underutilization of plexus blocks can be a result of lack of familiarity (and/or availability) of peripheral nerve block equipment: few of our respondents had seen or used a peripheral nerve stimulator but the majority believed that peripheral nerve blocks should not be done without one. Rudkin and Micallef⁸ reported that lack of anatomical knowledge or technique was the major

barrier for performing fewer than 10 ankle blocks per annum in Australia. Limited exposure to techniques and equipment was pivotal in this survey. It is encouraging that our respondents believe that peripheral nerve blocks will assume a greater role in their future practice, which is consistent with the growing popularity of plexus blocks in Europe and the United States.^{5,9}

This survey shows that there is enthusiasm for regional anesthesia among anesthesiologists in Nigeria, and the availability of equipment, including peripheral nerve stimulators, may encourage more use of plexus blocks. Affiliations with American, European, and Asian societies may promote regional anesthesia through the organization of workshops and symposia, as well as assist with the development of a teaching model for training in regional blockade.

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Single-Injection Percutaneous Peribulbar Anesthesia with a Short Needle as an Alternative to the Double-Injection Technique for Cataract Extraction

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BACKGROUND: We evaluated the efficacy of a single-injection technique for percutaneous peribulbar anesthesia with a short needle as an alternative to the double-injection technique for cataract extraction.

METHODS: We included 200 patients who underwent elective cataract surgery randomized into 2 equal groups. They received either single-injection peribulbar anesthesia with a 16-mm needle or double-injection peribulbar anesthesia with a 25-mm needle.

RESULTS: Both techniques provided comparable akinesia. A similar number of patients in each group required supplementary injection. The total volume of local anesthetic used was less in the single-injection group. There were no serious complications in the 2 groups.

CONCLUSION: The single-injection technique for percutaneous peribulbar anesthesia with a short needle is a suitable alternative to the double-injection technique for cataract surgery.

(Anesth Analg 2010;110:245-7)

Peribulbar anesthesia remains a popular choice for patients undergoing cataract surgery.¹ Several studies have demonstrated that peribulbar anesthesia provided optimal conditions for cataract surgery.² Furthermore, the injection of local anesthetic external to the muscle cone may decrease the likelihood of optic nerve and globe perforation.³ These potential benefits led us to evaluate the efficacy of a single-injection technique for percutaneous peribulbar anesthesia with a short needle, as described by Rizzo et al.,⁴ as an alternative to double-injection peribulbar anesthesia for cataract surgery.

METHODS

After obtaining approval of the Institutional Ethical Committee and written informed consent from all patients, 200 adult patients (ASA physical status I or II) scheduled for elective cataract surgery by phacoemulsification were enrolled in this prospective, single-blinded, randomized study. This study was performed in the Magrabi Eye & Ear Hospital in

Oman between January and December, 2008. Standard monitoring and IV access were placed in the preoperative holding area. The local anesthesia solution used was 0.75% ropivacaine plus hyaluronidase 15 IU/mL. The patients were randomly allocated using a sealed envelope technique to 1 of 2 equal groups to receive either the single-injection technique peribulbar anesthesia (single-injection group) with a 25-gauge, 16-mm, short-bevel needle or the double-injection technique peribulbar anesthesia (double-injection group) with a 25-gauge, 25-mm, short-bevel needle.

In the single-injection group, the injection site was percutaneous in the inferior margin of the orbit and in the same line with the inferior lacrimal canaliculus. The needle was advanced in an anteroposterior direction for half of its length and then obliquely in the direction of the optical foramen, as described by Rizzo et al.⁴ After negative aspiration, 5–7 mL of the local anesthetic solution was slowly injected. In the double-injection group, the first injection of 4 mL of the local anesthetic was done percutaneously at the junction of the lateral third and medial two-thirds of the lower orbital margin, and the second injection of 4 mL was given percutaneously just lateral to the supratrochlear notch. Mechanical orbital compression was then applied for 10 min in both groups, using a Honan balloon set at 30 mm Hg.

All measures were assessed by an observer who was blinded to the technique. Akinesia was evaluated in the 4 quadrants using a 3-point scoring system: 0 = akinesia, 1 = partial akinesia, and 2 = normal movement, giving a maximal score of 8 for the 4 muscles.

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Table 1. Demographic, Surgical, and Anesthetic Characteristics

| | Single-injection group (n = 100) | Double-injection group (n = 100) |
|---|-------------------------------------|-------------------------------------|
| Age (yr) | 60.65 ± 7.84 | 62.65 ± 8.05 |
| Sex (M/F) | 44/56 | 47/53 |
| ASA physical status (I/II) | 58/42 | 46/54 |
| Weight (kg) | 75.25 ± 6.80 | 77.10 ± 7.18 |
| Duration of surgery (min) | 33.91 ± 5.98 | 35.71 ± 7.59 |
| Axial length (mm) | 22.94 ± 1.60 | 22.54 ± 1.38 |
| Surgery side (right/left) | 47/53 | 59/41 |
| Onset of successful block (min) | 10.05 ± 1.81 | 10.40 ± 2.42 |
| Total volume injected (mL) ^a | 7.20 ± 0.77 | 8.48 ± 1.10 |
| Number of patients (%) required supplementary injection | 7 (7%) | 16 (16%) |

Data are displayed as means ± SD or percentages.

^a P = 0.001 compared with the single-injection group.

An akinesia score of 3 or less was defined as a successful block.⁵ If inadequate motor blockade (akinesia score >3) of 1 or more of the components of ocular motion was observed 15 min after block, supplementary anesthesia (3 mL) was injected into the involved quadrant using the same length needle as for the primary block. Additional assessments were then performed 5 min later. Any complications were recorded. The patient was asked immediately after the end of surgery to assess the degree of pain caused by the injection using a 10-point scale.

The statistical analysis of our results was conducted using the computer program SPSS version 15.0 for Windows (SPSS, Chicago, IL). Data were expressed as mean ± SD or percentages. The 2-way repeated-measures analysis of variance was used to compare the interval data, and Student's *t*-test was used as the *post hoc* test to determine differences between and within groups. χ^2 test was used to compare nominal data or percentages. Bonferroni correction for repeated comparisons was applied if necessary. *P* < 0.05 was considered significant, and *P* < 0.1 was defined as a tendency toward a significant difference.

RESULTS

The total volume (milliliters) of local anesthetic used was significantly less in the single-injection group compared with the double-injection group. The percent of patients who required supplementary injection was comparable in both groups (Table 1). Both techniques provided similar successful akinesia after 10 min (87% vs 76%) and 15 min (93% vs 84%) in the single-injection group and the double-injection group, respectively. There were higher percentages of patients who experienced moderate and severe pain in the double-injection group compared with the single-injection group (Table 2). There were no serious complications in the 2 groups that made it necessary to cancel the case or to give general anesthesia.

DISCUSSION

Our results demonstrated that both techniques are similar in terms of efficacy (both groups had a comparable adequate akinesia and percent of patients who required supplementary injection), with a lower total volume of local anesthetic in the single-injection group. These findings are in agreement with those of Mahfouz and Katheri,⁶ Clausel et al,⁷ and Riad and Nauman.⁸ Previous studies using B-scan ultrasonography to determine the exact pattern of distribution of the injectate in peribulbar anesthesia^{4,9} reported that a small volume of local anesthetic (5–6.5 mL) injected in this space is adequate to surround the eyeball and produce analgesia. The circumferential diffusion of the local anesthetic with the addition of hyaluronidase to sub-Tenon's space where the extraocular muscles and sensory and motor nerves of the eye are located explains the adequate akinesia achieved and the higher incidence of chemosis in the single-injection group.¹⁰

Needle length is an important consideration in needle-related complications. The relatively short needles (16 or 25 mm) used in single- or double-injection techniques, respectively, were associated with a low incidence of needle-related complications (hematoma and globe perforation) in both groups. Moreover, the shorter needles were associated with a

Table 2. Recorded Complications and Pain Caused During Injection of Local Anesthetic

| | Single-injection group (n = 100) | Double-injection group (n = 100) | P |
|--|-------------------------------------|-------------------------------------|--------|
| Chemosis | 16 patients (16%) | 5 patients (5%) | 0.011* |
| Subconjunctival hemorrhage | 9 patients (9%) | 2 patients (2%) | 0.030* |
| Retrolbulbar hemorrhage | 0 patients (0%) | 0 patients (0%) | 1 |
| Eye perforation | 0 patients (0%) | 0 patients (0%) | 1 |
| Pain during injection using a 10-point scale | | | |
| No pain (0) | 0 (0%) | 0 (0%) | |
| Mild pain (1–3) | 81 (81%) | 47 (47%)* | 0.001 |
| Moderate pain (4–6) | 16 (16%) | 42 (42%)* | |
| Severe pain (7–9) | 3 (3%) | 11 (11%)* | |
| Intolerable pain (10) | 0 (0%) | 0 (0%) | |

Data are displayed as number of patients and percentages.

* Compared with the single-injection group.

lower incidence of moderate and severe pain in patients undergoing the single-injection technique.⁶ The higher incidence of subconjunctival hemorrhage in the short-needle technique is attributable to the restriction of bleeding to the anterior orbit.

We conclude that the single-injection technique for percutaneous peribulbar anesthesia with a short needle is a suitable alternative to the double-injection technique peribulbar anesthesia for cataract extraction. This technique has the advantages of being simple and easy to perform with less pain, using a decreased volume of anesthetic, requiring a single rather than multiple punctures, and providing comparable adequate akinesia.

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Thoracic Paravertebral Block Using Real-Time Ultrasound Guidance

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BACKGROUND: We developed a technique for ultrasound-guided paravertebral block, which was subsequently applied in the clinical setting.

METHODS: An initial cadaver study was used to develop a technique that was used in the clinical setting on patients undergoing breast cancer surgery.

RESULTS: Paravertebral catheters were correctly placed in the cadaveric trial in 8 of 10 attempts. In the clinical study, all blocked patients ($n = 9$) had evidence of thoracic wall sensory block and analgesia postoperatively.

CONCLUSIONS: Determined by anatomical dissection, we have described the ultrasound features of the thoracic paravertebral space and performed clinically successful ultrasound-guided paravertebral block.

(Anesth Analg 2010;110:248-51)

Thoracic paravertebral block results in an ipsilateral somatic motor and sensory nerve block of multiple contiguous thoracic dermatomes above and below the site of injection.¹ Locating the paravertebral space can be technically difficult in part because it requires location of the transverse process by blind needle placement and has an overall failure rate of >10%.² Failure to identify the transverse process results in several needle redirections causing pain and discomfort and increases the potential risk of pneumothorax.

The use of ultrasound offers the capability to place a catheter in the paravertebral space with real-time image guidance. Sonographic measurements obtained using ultrasound scanning of vertebral transverse processes and parietal pleura can give an accurate measurement of the depth from the skin to the paravertebral space.³ Herein, we describe a new technique for ultrasound paravertebral block. An initial cadaver study was performed to provide a description of the sonographic anatomy of the

paravertebral space, and a subsequent clinical observation assessed patients' pain and satisfaction after this ultrasound-guided paravertebral block.

METHODS

An embalmed male cadaver (age at death 75 yr, height 175 cm, and body mass index 31.1) was selected for study of ultrasound characteristics of the paravertebral space. With the cadaver prone, 5 thoracic paravertebral regions on each side were scanned using a linear array transducer of 10 MHz (SonoSite Titan, Bothell, WA). For each space, the examiner attempted to identify the transverse process, the superior costotransverse ligament, and the paravertebral space, and using real-time imaging, inject dye or place an epidural catheter into 1 of these targets.

A blinded anatomist then performed a dissection of the paravertebral region at each level, in a layer-by-layer fashion. For each paravertebral space, the locations of the dye and catheters were identified, photographed, and referenced with the intended target structures.

With institutional ethical approval and written, informed patient consent, 10 ASA physical status I and II patients undergoing mastectomy or wide local excision \pm lymph node sampling \pm axillary clearance were studied.

While in a seated, kyphotic posture, baseline pain was assessed using a verbal rating scale before midazolam up to 0.05 mg/kg was administered for anxiolysis as clinically indicated.

The third thoracic vertebral level was identified by palpating and counting down from vertebra prominens (C7) and using a 38-mm broadband

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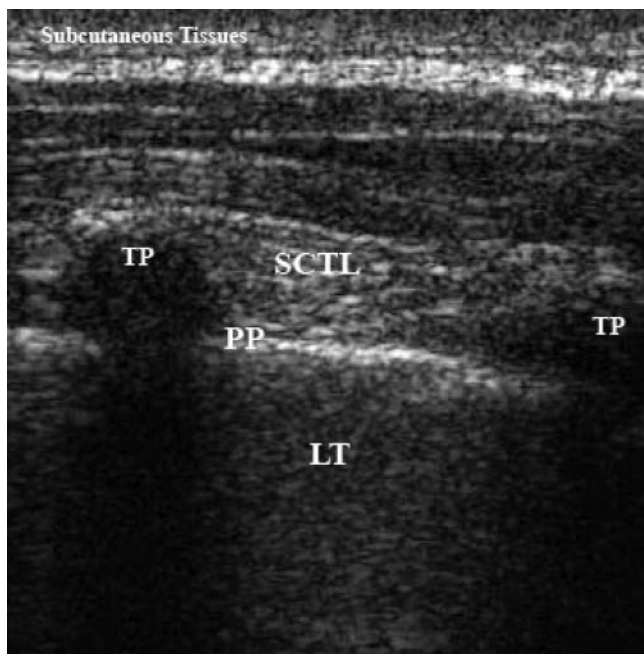


Figure 1. Ultrasound anatomy of a paravertebral space. Two dark lines demonstrate contiguous transverse processes with the paravertebral space found between the superior costotransverse ligament and the underlying parietal pleura. LT = lung; PP = parietal pleura; SCTL = superior costotransverse ligament; TP = transverse process.

(5–10 MHz) linear array transducer placed initially at a point 2.5 cm lateral to the tip of the spinous process in a vertical orientation, obtaining a sagittal paramedian view of the transverse process, superior costotransverse ligament, and underlying pleura (Fig. 1). The parietal pleura was identified as a bright structure running deep to the adjacent transverse processes, distinct from the deeper lung tissue, which could be seen to shimmer and move with patient respirations. The superior costotransverse ligament, less distinct, could be seen as a collection of homogeneous linear echogenic bands alternating with echo poor areas running from 1 transverse ligament to the next.

The midpoint of the transducer was aligned midway between the 2 adjacent transverse processes, local anesthesia infiltrated at its lower border, and an 18-gauge Tuohy needle introduced in a needle-in-plane approach in a cephalad orientation. The paravertebral space was entered midway between the 2 transverse processes avoiding bony contact. The tip of the needle was advanced under direct vision to puncture the costotransverse ligament. Saline (3 mL) was then injected deep to the superior costotransverse ligament to (a) demonstrate the position of injectate deep to the ligament, and (b) allow easier passage of the catheter, to a distance of 2–3 cm beyond the needle tip.

The time taken for the block was recorded, from the initial scanning point up to the point of securing the

catheter. An initial test dose of 3 mL of 2% lidocaine with 1:200,000 epinephrine was followed by 0.25% bupivacaine (0.3 mL/kg), administered over 10 min, after recording arterial blood pressure.

Before induction of anesthesia and 20 min after paravertebral block, sensory block was assessed by bilateral application of pinprick to the chest wall in the midclavicular lines, and patients' pain and satisfaction related to the paravertebral block were assessed using a verbal rating scale pain score and a satisfaction score (0 = dissatisfied, 10 = satisfied), respectively.

General anesthesia was induced with fentanyl 1–2 $\mu\text{g}/\text{kg}$ and propofol 1–3 mg/kg and maintained with sevoflurane in 50% oxygen/nitrous oxide. Tracheal intubation was facilitated using atracurium 0.5 mg/kg. Patients received paracetamol 1 g and sodium diclofenac 100 mg per rectum. In the event of block failure (defined as sustained heart rate or mean arterial blood pressure increase >10% of preincisional value for 5 min or longer), patients received morphine 0.1 mg/kg.

Patients were transferred to the recovery room, and a paravertebral infusion was prescribed (0.25% bupivacaine at 5 mL/h), continued for up to 24 h postoperatively. Patients were assessed for pain and presence of a sensory block in the recovery room and on the first postoperative day, where patients rated their overall perioperative experience using a satisfaction scale (0 = completely dissatisfied, 10 = completely satisfied).

RESULTS

In the cadaver, 9 of 10 paravertebral spaces and targeted structures within were identified as transverse process, superior costotransverse ligament, and paravertebral space. A clear image of the 10th space was not achieved. Figure 2 demonstrates a typical paravertebral space and Figure 1 depicts the corresponding ultrasound image of the paravertebral space. Needles were successfully placed into the intended targets in 8 of 9 attempts.

In the clinical study, 5 women underwent wide local excision with axillary sampling, and the remaining 5 patients had a radical mastectomy and axillary clearance. Nine women (median [range] age 54.5 [42–76] yr and weight 70 [60–83] kg) had paravertebral catheters placed preoperatively. The 10th patient was withdrawn because of a fainting episode during the block performance. The mean (SD) block time (from initiating scan until completion of catheter fixation) was 523 (211) s.

Sixty-six percent of patients had either complete or partial sensory loss measured at mean (SD) 20 (4.8) min after block performance, increasing to 100% in the recovery room. The quantitative number of levels blocked was not recorded. Three of nine patients (1 wide local excision and 2 mastectomy), all of whom

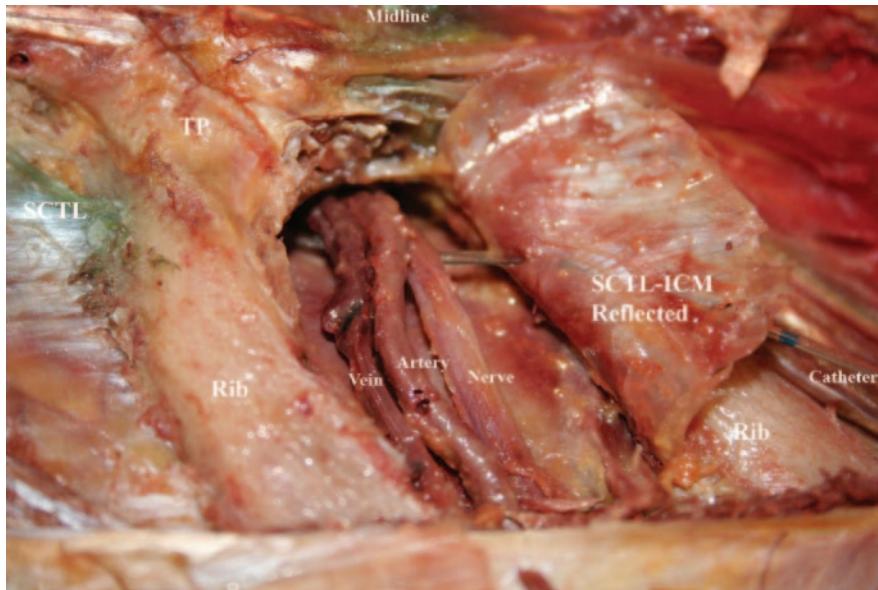


Figure 2. Cadaveric specimen after dissection demonstrating the anatomy of the paravertebral space. An epidural catheter is clearly seen to enter the paravertebral space, through the reflected transverse ligament. SCTL = superior costotransverse ligament; SCTL-ICM = superior costotransverse ligament, intercostal membrane complex.

Table 1. Median (Range) Pain, Comfort, and Satisfaction Scores for PVB and Surgery

| | <i>n</i> = 9 | Verbal rating scales (0–10) |
|-------------------------------------|--------------|-----------------------------|
| Preoperative pain | | 0 (0–2) |
| PVB pain | | 4 (0–7.5) |
| PVB comfort | | 7 (0–10) |
| Intraoperative morphine | | |
| Yes | 3 | |
| No | 6 | |
| VRS pain (in recovery room) | | |
| At rest | | 0 (0–8) |
| On movement | | 1 (0–8) |
| VRS pain (24 h postoperative) | | |
| At rest | | 0 (0–3) |
| On movement | | 1 (0–3) |
| Satisfaction (VRS measured at 24 h) | | 9 (4–10) |

PVB = paravertebral block; VRS = verbal rating scale.

had sensory block preoperatively, were administered morphine intraoperatively, with a median (range) postoperative pain score of 0 (0–8) (Table 1). Two of nine (1 wide local excision and 1 mastectomy) used their patient-controlled analgesia device, with a median (range) morphine consumption of 6.5 (4–9) mg over the 24-h study period.

DISCUSSION

In the anatomical portion of this study, we obtained clear sonographic images of the thoracic paravertebral space, linking them directly to their anatomical structures at dissection. Based on these findings, we subsequently described a real-time ultrasound-guided paravertebral block, which was successful in a clinical pilot study. The technique resulted in a successful block in 8 of the 9 patients in whom it was attempted.

A consistent ultrasonographic appearance was demonstrated during the study, which was thought

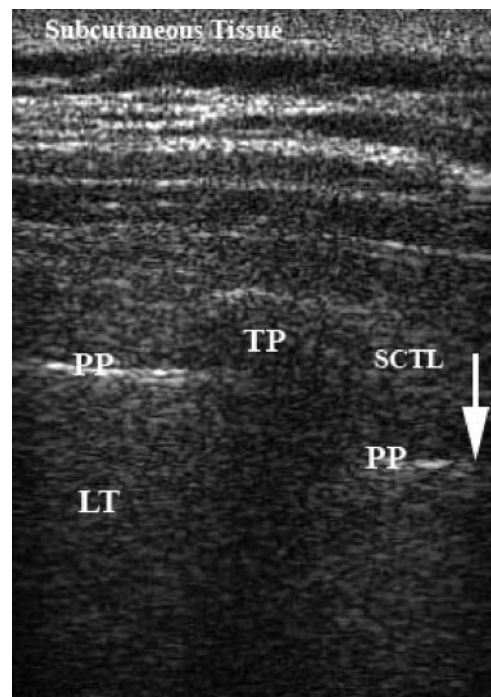


Figure 3. Ultrasound image of a paravertebral space after injection of saline-local anesthetic. The arrow highlights the displacement of the parietal pleura as the paravertebral space is filled with fluid. LT = lung; PP = parietal pleura; SCTL = superior costotransverse ligament; TP = transverse process.

to be a characteristic sign of accurate placement of the needle in the paravertebral space. As the tip of the needle was advanced under direct vision to puncture the superior costotransverse ligament, injection of saline into the paravertebral space led to an anterior displacement of the parietal pleura (Fig. 3).

A technical difficulty with this technique is potential loss of image of the needle tip as it is advanced. This is due to the acute angle the needle must take to enter between adjacent transverse processes. Tissue

disturbance may facilitate tracking of the needle tip in these circumstances.

Obvious limitations in both the anatomical and clinical elements of this study were the limited numbers studied and the lack of a control group. Further work will be required in a blinded comparative study of the traditional loss-of-resistance technique with our ultrasound-guided block.

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Ultrasonography as a Preoperative Assessment Tool: Predicting the Feasibility of Central Neuraxial Blockade

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A woman with severe ankylosing spondylitis presented to the preanesthetic clinic before total hip arthroplasty. She had required general anesthesia with fiberoptic intubation after failed attempts at spinal anesthesia for previous hip surgery. Using a portable ultrasound unit, we identified an open L4-5 interlaminar space and offered the patient an ultrasound-guided spinal anesthetic. Dural puncture with a single needle pass was subsequently achieved with the aid of preprocedural ultrasound imaging. Ultrasound may be a useful preoperative assessment tool for assessing the feasibility of central neuraxial blockade when technical difficulty is anticipated.

(Anesth Analg 2010;110:252-3)

Central neuraxial blockade using the traditional landmark-guided technique can be extremely challenging, if not impossible, in patients with abnormal spinal anatomy. Ultrasonography of the lumbar spine may facilitate successful central neuraxial blockade in such patients, by indicating the presence and location of a soft tissue window into the vertebral canal.¹⁻³ We describe the preoperative use of ultrasound in the anesthetic management of a patient with ankylosing spondylitis and a history of unsuccessful spinal anesthesia.

CASE DESCRIPTION

A 40-yr-old woman (height 175 cm, weight 70 kg, body mass index 22.9 kg/m²) presented to the preanesthetic assessment clinic before an elective right total hip replacement. She had severe ankylosing spondylitis that severely restricted the range of motion in her cervical and lumbar spine. There was no cardiopulmonary involvement. Radiological studies done 2 mo previously revealed solid ankylosis of the facet joints between the second and fifth cervical vertebrae, obliteration of most of the lumbar facet joints, bridging syndesmophytes between all lumbar vertebrae, and loss of lordosis (Fig. 1). She presented for a left total hip replacement a week after these studies had been done, and spinal anesthesia was attempted. A review of the anesthetic chart revealed that this was ultimately unsuccessful after multiple attempts by 3 experienced regional anesthesiologists, using 3 different approaches (midline, left, and right

paramedian) at 2 different intervertebral spaces (L3-4 and L2-3) and several needles (including a Tuohy epidural needle). General anesthesia was administered and intubation was achieved with the aid of a fiberoptic bronchoscope after an initial failed attempt using a GlideScope® (Verathon, Bothell, WA).

In light of this history, we performed a focused ultrasound examination of her lumbar spine in the preanesthetic clinic to determine whether ultrasound-assisted spinal anesthesia might be feasible. The patient's lumbar spine was scanned with a SonoSite M-Turbo™ (SonoSite, Bothell, WA) portable ultrasound unit and a low-frequency (2-5 MHz) curved-array transducer. With the ultrasound beam oriented in a longitudinal parasagittal (LP) plane, we were able to identify the intervertebral levels between the L2 and S1 vertebrae. It was evident from the scan that the L2-3 and L3-4 interlaminar spaces were extremely narrowed (Fig. 2A), and we were unable to visualize the ligamentum flavum (LF), dura mater (D), or posterior vertebral body (PVB) in either the LP or transverse midline (TM) plane. The L4-5 interlaminar space, however, was of normal width (approximately 1 cm) on the LP scan, and we were able to clearly see

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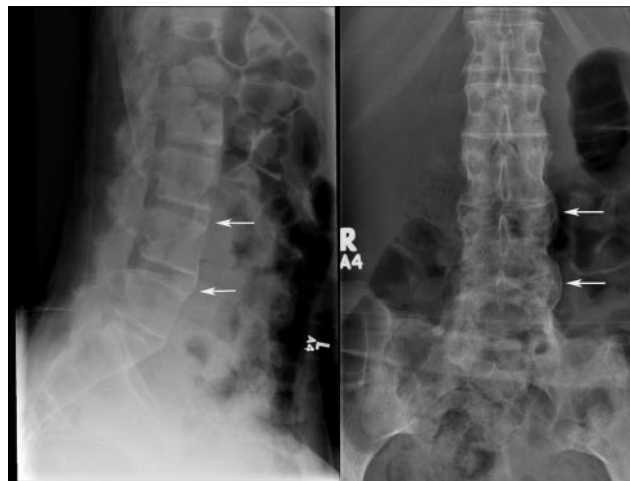


Figure 1. Lateral and anteroposterior radiographs of the patient's lumbar spine. There is loss of the normal lumbar lordosis and bridging syndesmophytes between the vertebrae (arrows).

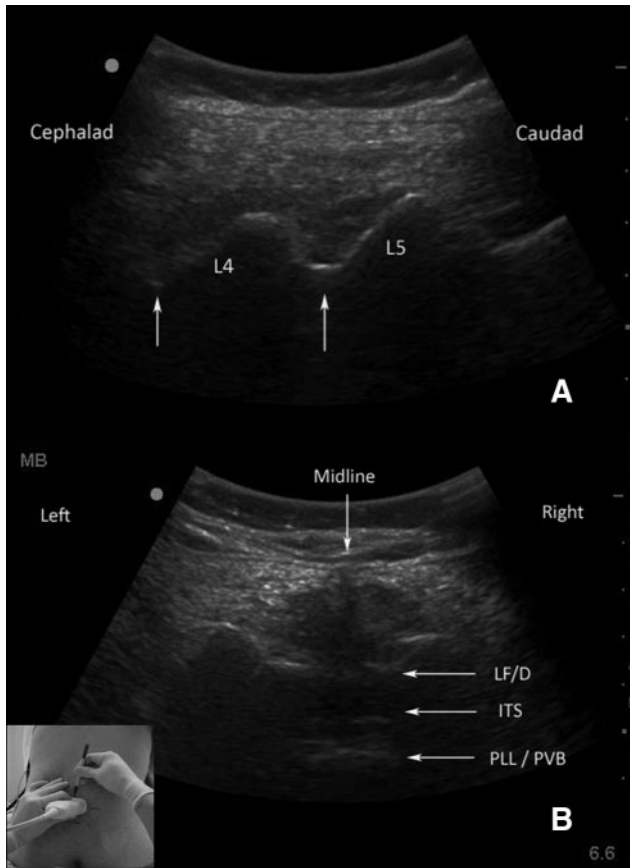


Figure 2. A, Longitudinal parasagittal ultrasound scan of the lumbar spine with a SonoSite™ M-Turbo portable unit. The laminae of the L4-5 vertebrae are visible as hyperechoic lines in a “sawtooth” pattern. The interlaminar spaces (arrows) are narrowed (<0.5 cm) at L3-4 but of normal width (approximately 1 cm) at L4-5. B, Transverse midline ultrasound scan of the L4-5 interlaminar space. All the relevant anatomical structures of the vertebral canal are visible: ligamentum flavum/dura mater (LF/D) complex, intrathecal space (ITS), posterior longitudinal ligament (PLL) overlying the posterior aspect of the posterior vertebral body (PVB). The location of the neuraxial midline and the L4-5 interlaminar space was marked as shown in the inset photograph. The spinal needle was inserted at the intersection of these markings.

the LF/D, intrathecal space, and PVB on the TM scan (Fig. 2B). We informed the patient that ultrasound-assisted spinal anesthesia appeared feasible at the L4-5 level.

On the day of surgery, the patient was brought to the block room, where IV access was secured and standard monitors were applied. She was placed in the sitting position, and her lumbar spine was scanned using a Philips HD11XE (Philips, Bothell, WA) cart-based ultrasound unit and a 2- to 5-MHz curved transducer. As before, we were able to easily visualize the LF/D and PVB on the TM scan at L4-5 but not at the L2-3 or L3-4 intervertebral level. The location of the neuraxial midline and the L4-5 intervertebral level was marked on the patient’s skin (Fig. 2). Dural puncture was successfully achieved with a 25-gauge Whitacre needle on the first pass, and 3 mL of 0.5% isobaric bupivacaine and 0.1 mg of morphine were injected intrathecally. The patient developed a sensory block to the T10 dermatome within 15 min. Surgery was uneventful and the patient made an excellent recovery.

DISCUSSION

The use of ultrasound to assist the performance of anesthesia-related procedures such as vascular access and peripheral nerve blockade is becoming commonplace. This case report illustrates the additional role that ultrasound may have in the preoperative assessment and anesthetic planning phase. General anesthesia in the patient with ankylosing spondylitis carries the risk of failed intubation and cervical spine injury, and awake fiberoptic intubation is recommended.⁴ On the other hand, technical difficulty and multiple attempts at central neuraxial blockade are associated with a higher risk of complications, including spinal hematoma.⁴⁻⁶ The information from the preoperative ultrasound scan allowed us to 1) confirm the feasibility of spinal anesthesia, 2) counsel the patient well in advance of her surgery as to her anesthetic options, and 3) formulate a management plan.

Preprocedural ultrasonography of the spine can supply much anatomical information pertinent to central neuraxial blockade, including the location of the neuraxial midline and interlaminar spaces, and the depth to the epidural space and intrathecal space.⁷ Although the routine use of ultrasound in central neuraxial blockade is probably unnecessary, we consider it invaluable in patients with abnormal spinal anatomy or poor surface landmarks.^{1,3} Fluoroscopic needle guidance is an alternative technique⁸; however, it has several limitations. First, its performance is confined to the operating room or radiological suite; second, both operator and patient are exposed to ionizing radiation; third, the prone position is usually required; and fourth, it is a relatively difficult technique to master. In conclusion, this case demonstrates that ultrasound may be a useful preoperative assessment tool for assessing the feasibility of central neuraxial blockade when technical difficulty is anticipated.

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Letters to the Editor

“Dry” Sevoflurane and the Falling Sky (or Lack Thereof)

To the Editor:

We suggest that the recent article by Kharasch et al.¹ regarding the various preparations of sevoflurane and their interactions with Lewis acids justifies neither the article's conclusions nor the alarm with which this information is being communicated.

Sevoflurane has been administered tens of millions of times with a single report of vaporizer-associated (Penlon Sigma Delta vaporizers) degradation by Lewis acids.² Not a single case of injury from sevoflurane degradation has been reported. In the *in vitro* study by Kharasch et al., conducted under artificial “accelerated” conditions (40°C and 15% humidity), only Penlon Sigma Delta vaporizers (as Kharasch et al. note, a vaporizer model that is both no longer sold and that Baxter has removed from service) degraded the lower-water sevoflurane preparations.¹ Importantly, degradation of sevoflurane at room temperature was not assessed in this experiment. The argument that “accelerated” stability conditions (40°C, 15% relative humidity) provides a government-sanctioned approach to testing does not make it good science. We have no evidence that it reflects what would happen to vaporizers at room temperature.

New Penlon Sigma Delta vaporizers are now “produced with a plastic (polytetrafluoroethylene) coated internal surface and all potential for Lewis acid production has been removed.”³ If correct (we have no reports of tests of the new Penlon vaporizer), then the issue of water content becomes moot for all present vaporizers, with the possible exception of older Penlon vaporizers remaining in circulation.

Dr. Mychaskiw is a member of the speaker's bureau for Baxter, Inc. and is a consultant to and has received research support from Baxter, Inc.

Statements regarding the safety of a drug, device, or medical therapy should be based on a balanced review of all available evidence. It is important that potential commercial bias not dictate our choice. In the past, we have criticized the use of our journals for both marketing purposes and incomplete disclosure of potential conflicts of interest.^{4,5} The article clearly communicated that Abbott financed, and Abbott employees participated in, the study at hand. However, we are uncomfortable that a company with a vested stake in the outcome of the research of another company's product had such a prominent role in the study.

We are also concerned about the cover illustration for the issue in which the article by Kharasch et al. appeared. The cover shows a “broken” sevoflurane vaporizer in an arid climate, accompanied by the bleached skull of a dead longhorn. We believe that makes the wrong statement. There is no known correlation between low-water sevoflurane and death.

In conclusion, journals must ensure as much objectivity as possible. We question whether the alarm regarding low-water sevoflurane raised by this report, and the accompanying cover, is consistent with the safety record and actual risk of low-water sevoflurane.

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In Response:

In contrast to the comment from Mychaskiw and Mayhew¹ that our data do not justify our conclusions,² we maintain that our conclusion—that lower-water sevoflurane underwent substantial degradation to hydrofluoric acid and other degradants during storage under accelerated stability testing in a Penlon Sigma Delta vaporizer—was unambiguously supported by all the data.

Mychaskiw and Mayhew argue that accelerated stability testing is a government-sanctioned approach that “does not make it good science.” Yet, they do not explain why. In fact, accelerated stability testing is an accepted scientific standard used throughout the pharmaceutical industry and governed by national and international regulation.

Although Mychaskiw and Mayhew aver that “we have no evidence that it (accelerated stability testing) reflects what would happen to vaporizers at room temperature,” we do know what happens at room temperature. As reported previously, low-water sevoflurane degraded in Penlon Sigma Delta vaporizers at room temperature to substances that caused corrosion and etching.^{3–6}

Mychaskiw and Mayhew are incorrect in their statement that there is only a “single report” of vaporizer-associated low-water sevoflurane degradation by Lewis acids. Sevoflurane degradation did occur clinically, multiple times, according to the reports. O'Neill et al.⁵ reported “the malfunction of a number of Penlon Sigma Delta vaporizers,” Gupta and Ely⁶ described 2 incidents, and the first Medicines and

Healthcare products Regulatory Agency notice (July 9, 2006) stated that "some units have been affected," whereas the second (November 22, 2006) states that the User Manual was updated because Penlon had become aware of "occasional production of certain degradation by-products." Neither Penlon nor the Medicines and Healthcare products Regulatory Agency dismissed the degradation, because the safety concern was substantial enough to trigger a vaporizer recall. Both the degradation of sevoflurane and the resulting physical corrosion of the Penlon Sigma Delta vaporizers with lower-water sevoflurane in our experiments are consistent with the corrosion reported under normal clinical (room temperature) conditions.³⁻⁶ These reports described corrosion involving the filling port shoe and sight glass. We believe that even 1 report of corrosion or degradation is important.

We are relieved that as Mychaskiw and Mayhew state, patient injury from sevoflurane degradation has not been reported. However, patient injury has not been required in prior instances of sevoflurane degradation to prompt a thorough analysis and reformulation to prevent such degradation.

Mychaskiw and Mayhew suggest that the entire issue of degradation is moot, because "the vaporizer is no longer sold, and Baxter removed it from service." In fact, the studies were designed and conducted while the vaporizer was being used and were underway when Penlon altered the manufacturing process to a plastic (polytetrafluoroethylene) coated internal surface (clearly stated in the article). However, older Penlon vaporizers may remain in circulation (as noted by Mychaskiw and Mayhew) and may be subject to Lewis acid degradation. Moreover, whereas the water content of sevoflurane (or content of any drug product) is clearly regulated by manufacturing specifications, the specific material components of vaporizers are not and

can change any time, and without any practitioner notification.

Mychaskiw and Mayhew question the data and suggest bias because the study was commercially sponsored. They are correct that the study was sponsored by Abbott. Anticipating such comments, and in the interest of data integrity and product quality, the studies were performed by an outside professional laboratory (PPD Development, LP, Middleton, WI) and under Good Manufacturing Practice standards.

Mychaskiw and Mayhew object to the cover art of the July 2009 issue of *Anesthesia & Analgesia*. As authors, we had no role in the decision of which article or what art was used for the journal cover.

Mychaskiw and Mayhew state that we "communicated with alarm" and infer that we claimed "the sky is falling" in the article. We did neither. Perhaps Mychaskiw and Mayhew object to our characterization of the low-water sevoflurane degradants as "hazardous," "dangerous," "toxic," and "corrosive." The most concerning degradant is hydrofluoric acid. The Material Safety Data Sheets for hydrofluoric acid from the Occupational Safety and Health Administration and others describe it as a "poison" and a "danger," "severely corrosive," "extremely hazardous," "toxic," and "may be fatal." Our conclusion was that low-water sevoflurane can degrade to hydrogen fluoride at concentrations that are known to be toxic.^{7,8} If practitioner vigilance resulted, then patient safety is served.

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In Response:

I appreciate Drs. Mychaskiw and Mayhew sharing their concerns¹ over the cover of the June issue of *Anesthesia & Analgesia*, which accompanied an article by Kharasch et al.² and an editorial by Max Baker.³ I also appreciate their raising the question about possible conflict of interest, given the role of Abbott in sponsoring the study.

Dr. Kharasch's article received considerable scrutiny in the peer review process. In addition to our internal reviewers, I sent his article to 2 very experienced chemists. The more I learned about sevoflurane's chemistry, the more alarmed I became. As Dr. Kharasch explains in his response,⁴ the risks of hydrofluoric acid are real. If sevoflurane is stored correctly, handled correctly, and used in an appropriate vaporizer, there should be no risk of

hydrofluoric acid formation, regardless of the water content. Those of us fortunate to practice in developed nations with access to modern equipment and pharmaceutical-grade sevoflurane have little reason to worry. However, one can purchase sevoflurane as a bulk chemical.⁵ There are descriptions of how to administer sevoflurane in developing nations using older vaporizers intended for other inhaled anesthetics,^{6,7} copper kettles,⁸ and with the nonspecific 885A field anesthesia machine.⁹ Perhaps it has never happened, but I can envision bulk desiccated sevoflurane in aluminum canisters being transported over hot dusty roads and then being administered using old halothane vaporizers by anesthesiologists unaware of these risks. The cover image was intended to increase sensitivity toward careful handling of sevoflurane, particularly in the absence of hydration. I am glad it caught the attention of Drs. Mychaskiw and Mayhew. That was my intent!

The article fully discloses that several authors are employed by Abbott and that Dr. Kharasch has been an occasional consultant to Abbott, the manufacturer of hydrated sevoflurane. Abbott's commercial interest in hydrated sevoflurane does not invalidate the findings. The methods are described in sufficient detail that Baxter, the manufacturer of the nonhydrated formulation, can repeat the study. If so, we would welcome their submission.

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False Confidences in Preoperative Pregnancy Testing

To the Editor:

If it is important to know whether a woman is pregnant before administration of anesthesia, then it is important to have confidence in her menstrual history, the results of her preoperative pregnancy tests, or both. Menstrual history is a challenge because recent studies demonstrate greater variability than previously assumed. Kahn et al.¹ correctly identify women of childbearing age by menstrual history rather than chronological age as many protocols do. The mean age of menarche is 12.5 yr (range, 8.0–16.2 yr) and for menopause is 51 yr (range, 31.5–61.2 yr).² The menstrual cycle is erratic in 72% of normal women; the median length is 28–29 days (range, 19–60 days) with greatest variability occurring in the years leading up to menopause.^{2–4} Faced with uncertain histories, it is not surprising that Kahn et al.^{1,5} sought clarity through routine preoperative point-of-care (POC) urine pregnancy testing.

Human chorionic gonadotropin exists in 2 forms, regular (hCG) and hyperglycosylated (hCG-H). The pituitary gland produces hCG during the run-up to menopause and placenta during pregnancy. In the first 4–5 wk of gestation, hCG-H is the predominant form.^{6,7} Currently available POC urine pregnancy tests, such

as the one used by Kahn et al.,¹ poorly detect hCG-H.^{4,6–9} They are not required by the Food and Drug Administration to do so.⁶ Despite advertising that they are 100% reliable on the first day of pregnancy,⁸ they may yield falsely negative results until Week 5 when hCG predominates and reaches the Food and Drug Administration–approved detection threshold of 20 IU/L.⁹ A patient may present 4 wk pregnant with a negative pregnancy test, undergo surgery, and then in Week 5 when her test becomes positive ask why an insensitive test was used.⁹

Quantitative laboratory serum tests detect both hCG and hCG-H with sensitivities of 1 IU/L. However, they are more expensive, more time consuming, less likely to yield false-negative results, and more likely to yield false-positive ones when the total serum hCG exceeds 5 IU/L, the threshold used to diagnose pregnancy, in newly recognized circumstances, e.g., sexually active nonpregnant women of childbearing age who have quiescent gestational trophoblastic disease,⁶ end-stage renal disease,¹⁰ or are unknowingly premenopausal in their mid-to-late 40s.¹¹ Then, there is the issue of "biochemical" pregnancies, i.e., those that implant, serum test positive, fail before Week 6 (60%), and delay menses briefly, or those that implant, urine test positive, and spontaneously abort after Week 6 (40%). It is estimated that more than 30% of gestations fail because of ineffective implantation or immune interactions.⁷

What conclusions can be drawn from this new information? First, an anesthesia provider should never tell a patient she is pregnant when her pregnancy test is reported positive. A gynecologist needs to discuss this result. Second, a patient may be pregnant despite a negative POC urine pregnancy test. Third, when informed consent, treatment guidelines and algorithms, and anesthetic decisions are based on pregnancy status, they must take into account the uncertainty embedded in the pregnancy test results.¹⁰

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In Response:

Every laboratory test has limitations. Bodin et al.¹ point out that the currently available urine pregnancy test is not 100% sensitive. Alternative testing methodology can increase sensitivity but at the cost of decreased specificity (more false-positive tests).

Interpretation of test results requires a pretest estimate of the probability of the condition being

tested for, in this case pregnancy, and knowledge of the sensitivity and specificity of the test. This is exemplified by patients 4 and 5 in Table 1.² These women each had a positive urine pregnancy test. Despite the inconvenience, their elective surgery was canceled to allow consultation with their gynecologist. These physicians thought that the positive urine human chorionic gonadotropin test was explained by other elements of their history, that they were not pregnant, and surgery could comfortably proceed.

We concur that a gynecologist, rather than the anesthesiologist, is the most appropriate physician to discuss the interpretation with the patient. Our hospital policy is to delay elective surgery when a test is positive so that the patient may consult with a gynecologist to interpret the test result.

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Estimation of Hemodynamic Parameters by Arterial Waveform: Available Technologies

To the Editor:

Funk et al.¹ present an interesting review concerning new minimally invasive technologies and devices available for measurement of cardiac output. In their review, Funk et al. did not consider 2 systems: the first is the Modelflow by Wesseling and co-workers² installed on the

Dr. S.M. Romano is the owner of the patent for the Pressure Recording Analytical Method (PRAM). Dr. S. Romagnoli declares that he has no competing interests.

Finometer® (Finapres Medical Systems, Amsterdam, The Netherlands); the second is the Pressure Recording Analytical Method (PRAM; used by MostCare®, Vytech Health, Padova, Italy) by Romano et al.^{3,4}

“Pulse contour methods” (PCMs) can be divided into 3 categories:

1. PCMs requiring an indicator dilution cardiac output measurement to calibrate the pulse contour;
2. PCMs requiring patient demographic and physical characteristics for arterial impedance estimation;
3. PCMs that work without any kind of calibration or pre-loaded data.

The PRAM is the only methodology belonging to category 3 because neither calibration nor adjustments based on experimental data are required.³⁻⁵ Therefore, PRAM is different than all the other PCMs including the more recent Flo Trac Vigileo® (Edwards LifeSciences, Irvine, CA) and LiDCOrapid™ (LiDCO Ltd, London, UK), which require preloaded patient's demographic and physical characteristics (age, height, gender, and weight), similar to Modelflow^{6,7} (category 2). For PRAM, the area under the systolic portion of the arterial wave is computed by considering both pulsatile and continuous contributions (A_{cp}). Stroke volume derives from the ratio between A_{cp} and the arterial impedance $Z(t)$ that is directly determined from the detailed analysis of the arterial wave sampled at high frequency (1000 Hz).³

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In Response:

In our review,¹ we attempted to cover those technologies that were widely available and for which a number of validation studies confirming their clinical efficacy in the perioperative environment were available.

Although the Modelflow concept described by Romagnoli and Romano² has been widely studied, its application on the Finometer has been less well researched in the perioperative period. Similarly, the Pressure Recording Analytical Method, an advancement of pulse contour technology, has not been well validated. We look forward to well-conducted validation studies on these devices and their clinical utility.

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Double-Lumen Tubes: Which Lumen for the Gum Elastic Bougie?

To the Editor:

We agree with Al-Metwalli et al.¹ that the gum elastic bougie (GEB) can be a very useful adjunct for correctly positioning a double-lumen endotracheal tube (DLT) into the proper mainstem. However, we fundamentally disagree with the manner in which the GEB was used. Al-Metwalli et al. inserted the GEB via the tracheal lumen. Our practice has been to advance the GEB through the bronchial lumen with a fiberscope inserted through the tracheal lumen.

Insertion of a left-sided DLT into the left mainstem bronchus is usually successful using well-known techniques.² On occasion, this can be difficult. In such an occasion, including intraoperative repositioning, we have used the method portrayed in Figure 1. Using the fiberscope to visualize the distal end of the DLT and carina, a well-lubricated GEB is passed (often

requiring several manipulations) via the bronchial lumen into the left mainstem bronchus. The DLT can then be advanced under direct visualization into the left mainstem taking advantage of the relatively stiff GEB for guidance. The procedure requires brief patient apnea, and an assistant helps to manipulate and position the tube.

In our opinion, using the GEB as described by Al-Metwalli et al., blindly advancing a DLT and bougie within a patient's trachea, risks severe injury. In other words, if the tip of the bougie was inadvertently directed against the posterior membranous wall of the trachea by the large DLT, it could conceivably tear the trachea with considerable morbidity.³

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In Response:

Stix et al.¹ described a technique aiding insertion of a left-sided double-lumen tube (DLT) into the left main bronchus by advancing the gum elastic bougie (GEB) through the bronchial lumen with a fiberscope inserted through the tracheal lumen. Although useful when advancing the tube into the left main bronchus is difficult, this technique is totally different than our modified DLT both in aim and application.² In our modified technique, we aimed to increase the success rate of initial DLT positioning. This facilitates quick lung isolation, particularly in some life-threatening

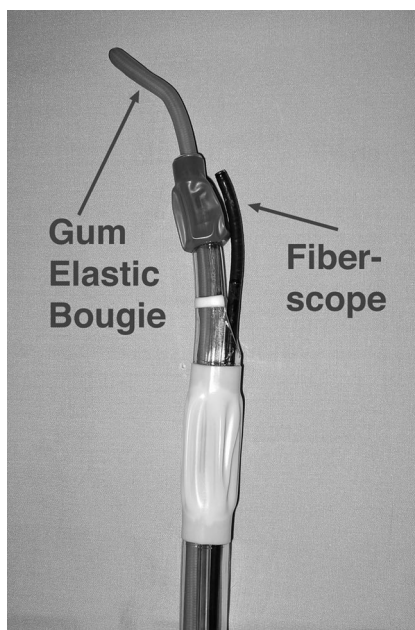


Figure 1. The photograph shows the gum elastic bougie inserted via the bronchial lumen and the fiberscope inserted via the tracheal lumen of a left-sided double-lumen endotracheal tube (DLT). The distal tip of the DLT and bougie can be visualized with the fiberscope. The DLT is advanced into the left mainstem bronchus with fiberoptic guidance.

situations, and shortens the time and effort of subsequent bronchoscopic adjustment.

In our technique, the GEB was not used for guidance but was modified and used as a retractable carinal hook. To do so, it was shortened and had its proximal end fitted with a 15-mm adaptor. Several precautionary steps were used with the newly fashioned GEB to avoid the problems described by Stix et al. or previously reported with hooked DLTs.^{3,4} These steps included 1) retaining the distal end of the GEB (the carinal hook) inside the tracheal lumen of the DLT during its insertion and rotation and allowing the tip to protrude out of the tracheal lumen only during advancement of the tube toward the carina, and 2) fitting a 15-mm adaptor to the proximal end of the GEB and marking the GEB so that when it is inserted into the tracheal connector of the DLT, it guarantees the proper length and direction of the protruded distal end of the GEB (the carinal hook).

In addition, we now recommend that the retractile hook should be manufactured from less-traumatic material than that used for a GEB or fashioned with a less-traumatic tip. Finally, although no complications were reported in our preliminary report, we recommend a larger study to verify the safety and reliability of the technique.

We share the belief of Stix et al. that the GEB is a useful gadget. However, the relevant question should be, What is the GEB used for? Different uses dictate different insertion methods and different lumens.

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Banana Blues

To the Editor:

In a recent article, Guay¹ reviewed 242 cases of methemoglobinemia related to local anesthetics and concluded that "Benzocaine should no longer be used." In an accompanying editorial, Weinberg² concurred, while still lamenting the occasional loss of the "banana room." Both authors point out that the Department of Veterans Affairs recently banned the use of benzocaine. Regrettably, the authors' conclusions and the Veterans Affairs' banning of benzocaine were not based on controlled studies but rather on case reports and no denominators.

Examining the sales of Cetacaine, a frequently used anesthetic spray that is a mixture of benzocaine (14%), tetracaine hydrochloride (2%), and butyl aminobenzoate (2.0%; the banana odor), however, yields a more realistic estimate of the incidence of methemoglobinemia caused by benzocaine (even ignoring other sources of benzocaine combinations). The manufacturer (Cetylite Industries, Pennsauken, NJ) has provided us with confidential sales data for 1990 to the present.* If we assume that only half the amount sold from 1990 through 2007 was sold during the previous 34 yr (from the beginning of manufacture in 1956 through 1989), we can estimate the number of possible doses or patient exposures. Each bottle contains 7.84 g of benzocaine, and each 1-s spray delivers 28 mg. Assuming that the recommended maximum 2-s dose is used, each bottle can theoretically deliver 140 doses. For our purposes,

*Personal communication, Stanley L. Wachman, President, Cetylite Industries, Pennsauken, NJ.

assume only 120 doses per bottle, resulting in approximately a possible 590,000,000 doses delivered during the period of Dr. Guay's report. For the sake of this discussion, assume that because of breakage, loss, or disposal of partially used bottles, only one-third of the possible doses was delivered to patients. This would result in 196,666,666 doses or patient exposures.

Dr. Guay found 54 reports of methemoglobinemia caused by benzocaine "in combination" from 1949 to 2007. Assuming that all of these cases were caused by the benzocaine in Cetacaine spray and that only 1 in 10 actual cases were reported in the literature,^{3,4} we estimate 540 cases of methemoglobinemia occurring as a result of using Cetacaine spray.

These conservative estimates suggest that the benzocaine in Cetacaine spray causes methemoglobinemia at the rate of 0.00027%, or 1 per 364,197 exposures. This rate is comparable to or better than the rates of adverse reactions of most over-the-counter and prescription drugs.^{5,6} Of the 2 reported adverse outcomes involving a benzocaine spray, 1 patient was 83 yr old and the other had complicating issues. In neither case is there information regarding possible overdose.

Benzocaine is minimally absorbed, has a rapid onset (1-2 min), has both a predictable and short duration (15-20 min), and its elimination is not dependent on direct hepatic metabolism. For these reasons, Cetacaine spray is an effective and popular topical anesthetic. Benzocaine-induced methemoglobinemia seems to be dose related,⁷ and we suspect that most cases of methemoglobinemia are due to overdose. It is believed that doses <1-2 mg/kg do not result in clinically significant methemoglobinemia.⁷ Therefore, the 2-s recommended spray (56 mg) would be safe for almost all adults. Certainly, extra care is indicated for the very young, the elderly, or patients either taking medications or with diseases predisposing to methemoglobinemia.⁸

We submit that Cetacaine spray, when used according to the manufacturer's recommendations and administered by qualified personnel, has a low rate of treatable adverse reactions. We have, based on the available numbers, intentionally overestimated the incidence of benzocaine-related methemoglobinemia by a factor of >60. Furthermore, if we were to assume that two-thirds, instead of only one-third of each bottle, was actually dispensed, the estimated incidence of methemoglobinemia would be nearly 1 in 1 million. All medications can produce adverse reactions. However, based on our analysis, we do not believe that the data support discouraging or banning the use of benzocaine products. Unfortunately, because there are numerous manufacturers, it is impossible for us to make any reasonable comparison of other local anesthetics' rates of adverse reactions when used in a similar manner.

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In Response:

Drs. Marcucci and Bourke¹ disagree that the use of benzocaine should be abandoned. Based on a fraction of the number of episodes reported (54 of 159) and the sales of some benzocaine products, they estimate that methemoglobinemia related to benzocaine would be an extremely rare event with an incidence of 1 in 1 million. Case reports are sent to medical journals by authors and accepted for publication by reviewers and editors only if they think that those cases can bring new knowledge or interesting educational reminders. Therefore, the number of episodes published has nothing to do with the true incidence of methemoglobinemia related to benzocaine. An incidence is best calculated from a large prospective study. Unfortunately, this is rarely available. Retrospective studies are our second best tool. From a high-volume transesophageal echocardiography laboratory, Novaro et al.² calculated that the incidence of methemoglobinemia related to benzocaine is 0.115% (95% confidence interval 0.037%–0.269% or 1 in 370 to 1 in 2700) for a first exposure and 0.345% (95% confidence interval 0.376%–3.531% or 1 in 28 to 1 in 266) if there are 2 exposures within 1 wk.

A large dose of benzocaine is not necessary to produce methemoglobinemia in susceptible individuals. Although some individuals will tolerate a large dose of benzocaine without ill effects, susceptible individuals (and it is not possible to know in advance who they are) may develop methemoglobinemia with the smallest dose that can be administered, which is a single spray. In my review, I identified 4 cases of methemoglobinemia occurring after a single spray, and this was also noted when the cases reported to the United States Food and Drug Administration were reviewed by Moore et al.³⁻⁷ The exact

amount of benzocaine administered is impossible to determine because it varies with the canister orientation and its residual volume.⁸ Therefore, there is no "safe dose" in susceptible individuals. The amount of methemoglobinemia produced with this minimal dose has been as high as 40%.⁵

The effects of methemoglobinemia should not be taken lightly. Apart from rendering a fraction of the circulating amount of hemoglobin ineffective for oxygen transport, methemoglobinemia will affect the oxygen-hemoglobin dissociation curve of the residual hemoglobin further limiting the amount of oxygen available to tissues.⁹ The heme in methemoglobin would be more likely to dissociate from the pocket in the protein, and heme release may trigger some inflammatory processes thus producing organ and tissue damage by mechanisms other than hypoxemia alone.¹⁰ Catastrophic outcomes may occur from methemoglobinemia even in previously normal individuals. A good example is the case reported by Ash-Bernal et al.¹¹ A 52-yr-old man investigated for dyspnea on exertion developed methemoglobinemia after the administration of benzocaine spray. Despite tracheal intubation and methylene blue administration, multiple organ failure and death ensued.

The question is, do we still really need benzocaine? The real efficacy of this drug can be seriously challenged by at least 2 randomized controlled trials in which benzocaine was either ineffective or no more potent than clove gel.^{12,13} I wrote: "Because it is impossible to predict which individuals will be susceptible to develop methemoglobinemia after benzocaine exposure, and also because there is no therapeutic window (between the doses required to produce a therapeutic effect and those producing toxicity) in susceptible individuals, the clinical use of benzocaine should be abandoned." And I maintain my statement.¹⁴

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Thromboelastometry to Guide Recombinant Activated Factor VII Therapy for Postoperative Refractory Intracranial Bleeding

To the Editor:

We describe management of postoperative bleeding in a neurosurgical patient in which rotation thromboelastometry (ROTEM[®], Pentapharm GmbH, Munich, Germany) was used to guide recombinant activated factor VII (rFVIIa) therapy.

A 54-yr-old man with no history of bleeding disorders underwent resection of a cerebellar hemangioblastoma. The procedure was complicated by massive bleeding (blood loss >5 L), for which 18 U of packed red blood cells and 6 U of fresh frozen plasma were transfused intraoperatively (a single Japanese unit is derived from 200 mL of whole blood). An intracranial hematoma compressing the brainstem formed on the second postoperative day requiring reexploration twice for hematoma removal. During the second reoperation, 6 U of fresh frozen plasma were transfused after which the following laboratory values were present: hemoglobin 10.8 g/dL, platelet count $138 \times 10^3/\text{mm}^3$, fibrinogen 441 mg/dL, prothrombin time international normalizing ratio = 1.24, and activated partial thromboplastin time = 30 s. Microbleeding persisted, however, despite all surgical efforts. We therefore performed ROTEM to assess the entire blood coagulation profile. The extrinsic pathway-activated ROTEM (EXTEM) demonstrated a marked prolongation in clotting time (CT), a prolonged clot formation time (CFT), and a decreased α angle (Fig. 1A, top; numerical data shown in Table 1). However, the intrinsic pathway-activated ROTEM (INTEM) trace was normal (Fig. 1A, bottom). The prolongation of CT seen only in the EXTEM implied that impaired functioning of factor VII, the coagulation factor initiating the extrinsic pathway, was, at least in part, responsible for the refractory bleeding.

We therefore administered 4.8 mg (70 $\mu\text{g}/\text{kg}$) of rFVIIa (Novoseven[®], Novo Nordisk, Copenhagen, Denmark) IV. Complete hemostasis was achieved immediately and no additional blood component therapy was required. A repeat EXTEM trace obtained after the treatment demonstrated a return to normal of the CT and CFT, as well as of the α angle (Fig. 1B, top). The INTEM trace remained unchanged (Fig. 1B, bottom). The patient subsequently recovered without thromboembolic or neurologic complications.

In this case, ROTEM was more useful in detecting the coagulation abnormality in the setting of massive bleeding and transfusion than were the standard coagulation tests. The usefulness of thromboelastography/thromboelastometry as a point-of-care coagulation monitor in guiding transfusion therapy has been discussed.¹⁻³ However, the significant discrepancy in CT between EXTEM and INTEM as seen in this case has not been documented. In our case, the normal INTEM trace implied that the functioning of intrinsic and common coagulation pathways was within the normal range at the time point. Furthermore, platelet count and fibrinogen level during the second reoperation were sufficient to expect normal hemostasis. Because a normal fibrinogen level is reported to be important for rFVIIa therapy to achieve hemostasis,^{4,5} we thought that rFVIIa therapy might be appropriate treatment in that the patient might be prepared to respond to it. The EXTEM trace obtained after the treatment demonstrated a return to normal of the CT and CFT.

Although our findings were not confirmed by measurement of the actual blood levels of coagulation factors, this case does suggest the usefulness of ROTEM as the point-of-care test of choice to guide rFVIIa therapy in the setting of refractory coagulopathy after massive bleeding and transfusion. It might, in other words, differentiate the bleeding diatheses expected to respond to rFVIIa therapy from those

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Thromboelastometry to Guide Recombinant Activated Factor VII Therapy for Postoperative Refractory Intracranial Bleeding

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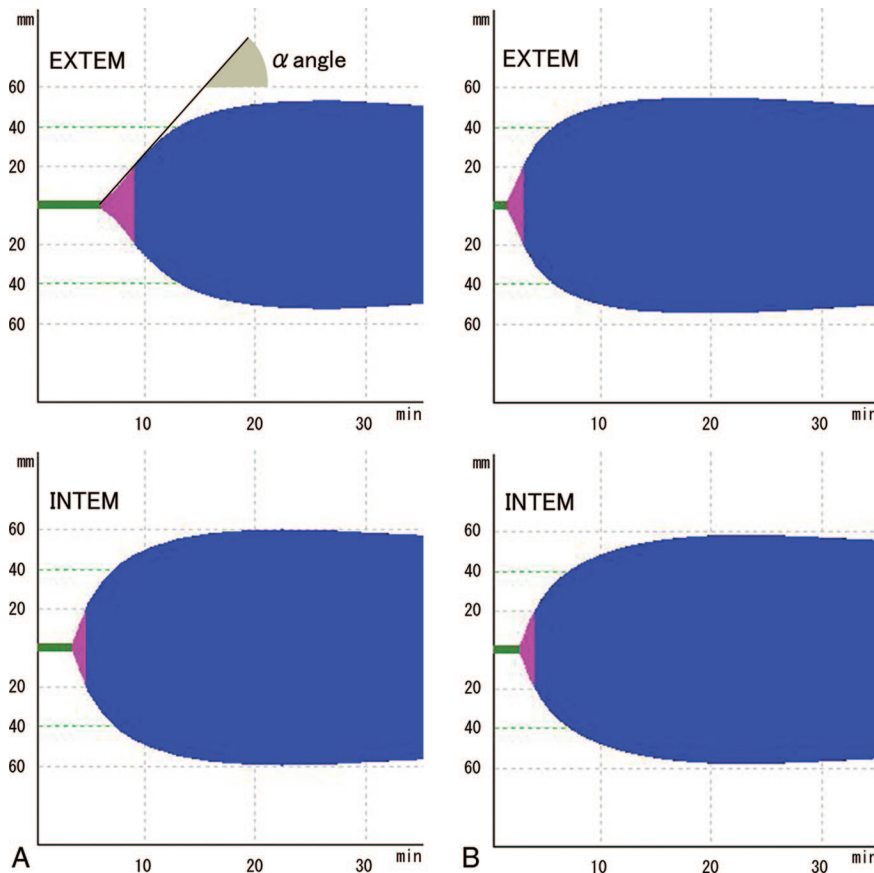


Figure 1. The ROTEM® (Pentapharm GmbH, Munich, Germany) traces. The amplitude of the clot strength is displayed in the vertical axis as a function of the time (horizontal axis). The INTEM and EXTEM are ROTEM tests in which the intrinsic and extrinsic coagulation systems are activated by adding phospholipid-ellagic acid and tissue factor, respectively, as reagents. Clotting time (CT, green) and clot formation time (CFT, pink) are defined as the duration until the amplitude of the trace reaches 2 and 20 mm, respectively. The α angle represents the speed of thrombin generation and of fibrin polymerization. Maximum clot firmness is the widest width within the trace. A, The EXTEM (top) and INTEM (bottom) before administration of rFVIIa. Prolonged CT and CFT were noted in the EXTEM. B, Treatment with rFVIIa was associated with normalization of CT and CFT in the EXTEM, whereas the INTEM remained unchanged.

Table 1. The Hemostatic Profiles Pre- and Posttreatment with Recombinant Factor VIIa

| Parameters (reference range) | Pretreatment | Posttreatment |
|------------------------------|--------------|---------------|
| Laboratory assays | | |
| PT/INR (9.9–12.4 s) | 12.9/1.24 | 9.8/0.81 |
| EXTEM | | |
| CT (35–80 s) | 353 | 80 |
| CFT (35–160 s) | 184 | 91 |
| α angle (63°–81°) | 56 | 72 |
| MCF (53–72 mm) | 52 | 58 |

MCF = maximum clot firmness; CFT = clot formation time; CT = clotting time; PT/INR = prothrombin time/international normalization ratio; EXTEM = extrinsic pathway-activated ROTEM.

for which other approaches are necessary before the rFVIIa administration by assessing both INTEM and EXTEM profiles. In conclusion, we observed a significant prolongation of the EXTEM-CT with normal INTEM-CT in the setting of massive bleeding in a neurosurgical patient. Administration of rFVIIa was associated with normalization of the EXTEM trace. ROTEM can be a beneficial tool to monitor the effect of this hemostatic agent. Additional studies are needed to help clinicians guide prohemostatic therapies.

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Book, Multimedia, and Meeting Reviews

Miller's Anesthesia, 7th ed.

Ronald D. Miller, Lars I. Eriksson, Lee A. Fleisher, Jeanine P. Wiener-Kronish, William L. Young, Philadelphia, PA: Churchill Livingstone, Elsevier, 2009. ISBN 978-1-4160-6624-8. 3084 pages, \$329 (Basic version), \$429 (Premium version).

Editing a major 2-volume, multi-authored textbook is such an arduous, challenging, time-consuming task that few academicians choose to undertake it. To be an effective editor, one must have a detailed knowledge of the discipline; an awareness of those in the discipline who are doing the innovative work and have the ability, time, and interest to describe the field in appropriate detail; and a dedication to collating and editing the material to avoid needless repetition. Finally, one must have the political savvy and sensitivity to deal effectively with authors whose contributions are inappropriately late or inartfully constructed. However, once the hurdle of the first edition is out the door, subsequent editions are usually only minor revisions of the original to incorporate new information.

Such is not the case with the 7th edition of *Miller's Anesthesia*. When compared with the 6th edition, the 7th is in many ways a new, 2-volume textbook that is so creatively constructed that it may obviate the need for an eighth edition. With the 7th edition, Dr. Ronald Miller has demonstrated that he has the skill to take a fresh, innovative, progressive view of anesthesiology as it currently exists and what it might look like in the future, and with the able assistance of 4 associate editors constructs a textbook that may be ageless. This overview is true not only for the Miller edition, but also for the Barash text *Clinical Anesthesia*, 6th edition, a review of which follows the Miller review.

Before examining the chapters in detail, an overview of the structural changes in this edition is necessary so that readers will know what they will be getting if they buy it, or what they will be missing if they do not. For a start, 96 new authors have been added, and the deletion of 36 results in a net gain of 60 authors, all of whom bring a fresh approach to the field. In addition, 33 of the new authors are from foreign countries, and with the addition of Lars Eriksson from Stockholm as an Associate Editor, this becomes the first truly international anesthesiology textbook.

With the world shrinking and becoming more interdependent, this is a much needed and welcomed move for our specialty. An especially valuable addition to this edition is the ability to access expertconsult.com on the Internet because it allows for continual updating of text as new information and ideas emerge. Most of the references in the texts are from 2007 or earlier, as would be expected considering the timeframe required to assemble an edition of this magnitude. However, with expertconsult.com, the authors can update their chapters as frequently as desired or indicated. This feature alone makes this edition ageless. Although the 7th edition has just been published, there are already 5 updates, dated June 4, 2009, dealing with obstructive sleep apnea, substance abuse among anesthesiologists, use of the BIS monitor and awareness, perioperative consideration of coronary stents, and preoperative statin therapy. The other valuable feature in expertconsult.com is the ability to view videos of technical procedures such as patient positioning, anesthesia machine checkout, use of the fastrach LMA, needle cricothyrotomy, and ultrasound guidance for vascular catheter placement or regional block placement. As a first pass, the videos are generally good, but with experience they can be improved. As examples, with the machine check, it is not clear whether the check relates to the Aestiva machine or is applicable to all anesthesia machines currently in use. The fastrach LMA video could be improved by such simple changes as "intubate the trachea" not the patient; eliminating the high "AH" count, stating that it is important to loosen the 15-mm connector to the tube before inserting the tube, so the struggle with this in the video is eliminated. Also, does the type of lubricant matter? The purpose of the metal handle is never mentioned, or how it is to be used to facilitate intubation of the trachea if the first pass should go into the esophagus. I believe that the needle cricothyrotomy video places more emphasis on this technique as a life-saving maneuver than is warranted either from the literature or from experience. Even in experienced hands and everything going smoothly, it will take several minutes to locate the kit, identify the target, and complete the task. If anything should go wrong, such as inability to find the trachea with a needle, which is common, or failure of the dilator to follow the wire, valuable

time is lost. A much quicker and more effective technique would be to take a knife, insert it into the cricothyroid membrane, twist the knife, and insert a tube. There is no serious risk with doing this and ventilation can be established almost instantaneously. In essence, I believe this video needs a more balanced and realistic approach. Finally, in the Aintree video, it is suggested that one can ventilate the lungs once it is in place using the 15-mm connector. One cannot establish any meaningful ventilation through an Aintree catheter, but one can insufflate oxygen, which should be the focus. The beauty of the videos on expertconsult.com is that they can be revised easily to correct flaws or incorporate new technology as it emerges. This is a great improvement over the video disk that accompanied the 6th edition.

There are many other substantial changes in the 7th edition that are worth mentioning. The first 10 chapters of the text are for the most part completely new or greatly revised from the 6th edition. In addition, they have been moved from the back of the text to the front, acknowledging at the outset the importance of existing and future challenges and how we might address them. These include emphasis on the need for research, evolving anesthesia practices worldwide, growing use of medical informatics to improve efficiency and safety, importance of quality improvement, human performance and patient safety, use of simulation in teaching, research, and for specialty recertification, and the current and emerging ethical and legal aspects of anesthesiology. The key points of each chapter have been moved from the back of the chapter to the front, so the reader can get a snapshot view of the issues in that chapter. A very substantial change is the number of new illustrations and tables included in both the new and revised chapters. The colors used in the illustrations have been changed from mostly red and white to primarily blue and gold (with occasional yellow, brown, or green), perhaps a subtle reminder that this book had its genesis at the University of California. The color change is striking, and through contrast greatly enhances the ease of interpretation and the readability of the illustrations.

The 2-volume edition is divided into 9 major sections: Introduction, Anesthetic Physiology, Anesthetic Pharmacology, Anesthesia Management, Adult Subspecialty Management, Pediatric

Anesthesia, Postoperative Care, Critical Care Medicine, and Ancillary Responsibilities and Problems. Within these 9 sections, there are 102 chapters, grouped according to interrelated subjects. There is a Table of Contents and complete Index with each of the volumes, so the reader can access all topics from either volume. The top and fore edge of the text blocks are color coded to facilitate finding the section of interest. The weight of the 2 volumes has been decreased from just under 18 lbs for the 6th edition to just under 16 lbs for the 7th. This weight loss has been accomplished in part by using a somewhat smaller type-set. The "basic version" of the 7th edition provides 2 volumes and access to the full text online, and is priced at \$329. The "premium version" provides the basic version plus the many additions noted above and is priced at \$429. Without question, I would urge the potential buyer to consider the premium version. The ability to receive timely revisions, updates, and new versions of the text and videos makes the extra \$100 a very smart investment in the future. Something that the editors might consider for the future is to include the e-mail addresses of the authors so that readers can communicate directly with them regarding unanticipated or outlier issues that always emerge with any topic.

It is impossible to review a textbook of this magnitude in chapter by chapter detail, so I will highlight the images that emerged while reading some chapters and perusing others. Overall, the editors have done an excellent job of minimizing duplicate material, although some repetition is desirable to allow for expression of different points of view. Section II on Anesthetic Physiology is highlighted by a new chapter that provides a comprehensive analysis of the anatomic sites and physiological functions of normal sleep, memory, and consciousness, and how they compare and contrast with the anesthetic state. This is followed by a chapter on the Autonomic Nervous System, which has much improved illustrations of the anatomy of the sympathetic and parasympathetic nervous system, a more detailed consideration of the neuropeptide transmitters and actions, and a good review of β -adrenergic blockade. The chapter on Cerebral Physiology contains an excellent discussion of the pathophysiology of cerebral ischemia and the status of brain protection. The chapter on Respiratory Physiology is written by a new author with a substantially different organization and content from the prior edition. Included is a discussion of respiratory function both awake and anesthetized, and review of

the relationship of airway size to lung volume, a key relationship that is often forgotten in reviews of bronchospasm. The author suggests that it might be appropriate to use less than maximal concentrations of oxygen during preoxygenation or during clinical anesthesia to minimize loss of lung volume or atelectasis, or consider using CPAP to mitigate the oxygen effects on lung volume. The Hepatic Physiology has been extensively revised and includes a greater focus on the gross and microscopic anatomy of the liver, perhaps due in part to the use of partial livers for transplantation. The Renal Physiology chapter is substantially revised, and contains a good review of renal toxicity of anesthetics. However, the author still clings to the recommendation that the total gas flow during sevoflurane anesthesia should be 2 L/m to eliminate the possibility of Compound A toxicity, despite the fact that sevoflurane has been administered to more than 250 million patients worldwide without any documented evidence of renal impairment from Compound A. Also, the chapter contains no mention of the effects, if any, of body position (prone, lateral, sitting) on renal function, perhaps because this is an unexplored issue.

Section III deals with the pharmacology of anesthesia. The first chapter provides an excellent synopsis of the basic principles of drug action using pharmacokinetic and pharmacodynamic modeling. This is followed by a new chapter on the molecular sites of anesthetic action, and where we are and need to go with our research into how anesthetics work. The Pulmonary Pharmacology chapter has an expanded section on ventilator mechanics and acute lung injury. There is also a section on bronchospasm, but it omits any discussion of the relationship of airway size to lung volume. The Cardiovascular Pharmacology section has an extensive update on anesthetic protection from myocardial ischemia. The chapter on delivery systems for inhaled anesthesia has been extensively revised to incorporate the anesthetic work stations with automatic machine checkout systems, no bellows visible in the ventilators, and new types of vaporizers. The 2007 checkout guidelines and additional checkout notes are provided. The chapter on opioids contains many new illustrations dealing with the pharmacology of opioids, drug interactions with opioids, and their use in total IV anesthesia and as transdermal patches. The section on neuromuscular blocking drugs (NMBs) provides a detailed discussion of sugammadex, as well as the expected pharmacology of NMBs. What does not

come across clearly is that the effectiveness of all nondepolarizing NMBs is dependent not only on dose administered, but also depth of anesthesia. Also, nothing is mentioned about not using rocuronium for priming because of the severe pain associated with its injection. Even alkalinizing the rocuronium with a small amount of sodium bicarbonate does not abolish the pain on injection. Finally, there is a new chapter on inhaled pulmonary vasodilators with a special emphasis on nitric oxide.

Section IV deals with Anesthesia Management and is the largest section in the 2-volume edition. It contains 25 interrelated chapters dealing with operating room care in the broadest sense. It includes an updated chapter on the Risk of Anesthesia as it relates to the location of surgery, the anesthesia provider, and the drugs and monitoring used. The chapter on Preoperative Evaluation is written by a new group of authors and represents an excellent source for learning how to establish an efficient preoperative clinic, formulating evidence-based evaluation protocols for various diseases to minimize last-minute cancellations, and use of electronic media to transfer information rapidly and accurately among caregivers. The chapter on Anesthetic Implications of Concurrent Diseases has been condensed and more than 500 references have been deleted. The chapter on Patient Positioning is totally revised, with new authors and much improved illustrations of patient positions and safety precautions. One oversight relates to the fact that no mention is made of the use of a wire-reinforced endotracheal tube when positioning a patient prone to avoid kinking of the tube if it exits the mouth at a right angle to the head-holder. The chapter on Malignant Hyperthermia has been rewritten by a new set of authors and logically incorporates a consideration of neuromuscular disorders. The remaining chapters on Monitoring Instrumentation, Monitoring Depth of Anesthesia, Cardiovascular, Renal, Respiratory, Neurologic, Neuromuscular, and Temperature Monitoring, Transesophageal Echocardiography, and Electrocardiography have all been updated and improved. This section concludes with chapters on Acid-Base Balance, Airway Management, Regional Anesthesia including use of ultrasound guidance, Fluid and Blood Therapy, and Coagulation. Despite rapidly changing technology, the chapter on Airway Management is current, comprehensive, and balanced in its approach to dealing with the difficult airway. The

chapter on Ultrasound Guidance for Regional Anesthesia is new, and the text and illustrations are excellent.

Section V is titled Adult Subspecialty Management, and includes 23 chapters that focus specifically on the unique or special anesthetic or patient requirements encompassing the whole spectrum of surgical procedures including cardiac, thoracic, bariatric, vascular, renal, or hepatic surgery, and transplantation, trauma care, or those undergoing laparoscopic, robotic, or laser surgery. Each of these operative procedures has their own special needs of which the competent anesthesia provider must be aware. Reading these chapters in advance of initiating an anesthetic plan will alert anesthesia providers as to what to anticipate and expect as the operation proceeds so that they can maximize their effectiveness as members of the surgical team.

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In summary, the 7th edition of *Miller's Anesthesia* could serve as a model for how to assemble a multi-authored text that is fresh, comprehensive, precise and articulate in content, evidence based, beautifully illustrated, and perhaps most importantly has the capacity to be revised as needed. The "Premium Edition" is not only a valuable resource to the current students and teachers of anesthesiology, but with the ability to update text and videos, could remain

a bible of anesthetic care for future generations.

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Clinical Anesthesia (6th Edition)

Paul G. Barash, Bruce F. Cullen, Robert K. Stoelting, Michael Cahalan, M. Christine Stock. Philadelphia, PA: Lippincott Williams & Wilkins, 2009. ISBN-10/ ASIN: 0781787637, ISBN-13/ EAN: 9780781787635. 1760 pages, \$199.

It is very unusual for anesthesiology to have 2 major textbooks published within a matter of a few weeks of each other, but this has happened, and it gives both this reviewer and potential buyers a wonderful opportunity to compare and contrast these 2 comprehensive anesthesia textbooks and determine which one best serves their clinical needs. There are many similarities and some striking differences between this new edition of *Clinical Anesthesia* and *Miller's Anesthesia* (7th Ed.). First, *Clinical Anesthesia* is a single-volume book with 1640 pages of text, illustrations, and references, weighing in at about 7.5 lbs. Although considerably more portable than the Miller 2-volume edition, it still does not lend itself to being carried about for quick review or referencing between cases. There are a total of 141 authors, most of whom are extremely well-known and recognized experts in the fields about which they are writing. Some authors contributed to both major textbooks but generally not in the same subject. About a third of the authors are new to this edition, which gives a fresh approach to those topics. This edition does not have the international flavor of the Miller edition in that there are only 4 foreign authors: 2 from Canada and 1 each from India and Thailand. This edition was edited by 5 very talented senior authors who are also experienced scientists and educators in anesthesiology. As a result, the chapters are tightly structured with a minimum of overlap or repetition. As much as possible, the authors and editors have tried to emphasize the clinical relevance of the scientific material being presented.

Barash and his coeditors have very wisely utilized the Internet to enhance the value of the textbook. Purchase of the book provides the owner with an access code to a bank of "add on" features. There is a text bank that allows the reader to obtain the complete text online. There is also a podcast bank that

allows the reader to download text to an iPhone, iPod, or Blackberry. There is a quiz bank of questions and answers relevant to each of the chapters. To my knowledge, the podcast and quiz banks are unique to the Barash edition. And finally, there is an image bank that is not yet available. Although the contents of this bank are not evident from reviewing the text, presumably it will include video images of technical procedures being performed. The Internet access will allow the authors and editors of *Clinical Anesthesia* to update and revise their contributions as necessary to keep the book timely and relevant to clinical practice.

There are a total of 60 chapters organized into 8 different sections. Each chapter starts with a brief itemization of the contents of that chapter followed by a list of key points that form the basis of the subsequent text. The key points are numbered, and these numbers reappear at the appropriate points in the text. The typeset is very readable, and most chapters have an abundance of colorful, well-designed illustrations that enhance the text. There seems to have been a conscientious effort on the part of the authors and editors to utilize references judiciously to substantiate their key points, and they are to be commended for this. A nice feature for the reader is that the major references are highlighted in the reference list for each chapter. Many of the key references are from 2007 or earlier, so updating will be necessary through the Internet to keep the book current.

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pharmacology of inhalation, IV and local anesthetic drugs, along with an incisive analysis of drug interactions in anesthesia. In the chapter on opioids, there is the perpetual warning that cycles from textbook to textbook that meperidine should be used with caution or not at all in clinical anesthesia because of the potential for accumulation of its metabolite, normeperidine, which may promote tremors, myoclonus, and seizures. This has resulted in almost complete abandonment of the use of meperidine during the perioperative period in this country and abroad. This is an example whereby the complications from an inappropriate use of a drug (e.g., treatment of cancer or chronic pain) may have tainted its use in an appropriate setting (e.g., operating room and postanesthesia care unit).

Section V focuses on preoperative assessment and preparation, including consideration of rare conditions such as malignant hyperthermia. The chapter on the anesthetic work stations gives an excellent review of the generic operations of anesthesia machines, circuits, vaporizers, and ventilators, but also the unique characteristics of those commonly used in the United States. This chapter also includes the 2008 American Society of Anesthesiologists' recommendations for preanesthetic checkout of equipment. Section VI addresses all of the issues related to anesthetic management including monitoring, positioning, airway management, regional anesthesia, the special needs of the elderly patient, and care of the trauma or burn patient. Included in this section are 2 excellent chapters that address areas of constant change, namely, the field of monitored anesthesia care, and the ever-expanding provision of anesthesia services in ambulatory and off-site facilities. Section VII is the largest section in the book, containing 16 chapters on the subspecialties of anesthesia. As would be expected, all surgical specialties are represented, and the specific needs and obligations of the anesthesia provider clearly delineated. The final section (VIII) contains a potpourri of topics including recovery room care, acute and chronic pain management, cardiopulmonary resuscitation, and disaster preparedness. Finally, there is a very useful appendix on electrocardiography illustrating all of the various rhythm abnormalities that one might encounter in anesthesia practice and, where applicable, the most appropriate treatment.

Now the really tough question . . . If one is forced to choose only 1 of these 2 new comprehensive textbooks, which one should the practicing anesthesiologist or physician-in-training purchase? Both new editions of these 2 familiar

textbooks are extremely well written, comprehensive, evidence-based, carefully edited, appropriately referenced, and both have utilized an abundance of well-crafted illustrations to emphasize the important issues. Most authors of chapters in both textbooks have attempted not only to report the facts but also more importantly to critique the facts. The depth of analysis of some topics is certainly greater in the Miller book because of the availability of 2 volumes. As well, the video systems in the Miller edition are well ahead of those in the Barash edition at this point in time. However, in the last analysis, both editions contain all the essential information necessary to become a competent anesthesia provider and/or successfully pass the written and oral examinations. If cost is a major consideration, I would recommend the Barash textbook, because it gives all of the important benefits of the Miller "basic edition" at a lower cost to the purchaser. If the price of the book is of lesser importance, then I would recommend the Miller "premium edition" because of its somewhat greater content and detail, and its more established video systems. However, the long-term value of either edition depends in large measure on the quality, frequency, and timeliness of the updates and revisions through the Internet, and the buyer has no ability to estimate those features with either of these new editions at this time.

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Society for Pediatric Anesthesia/American Academy of Pediatrics/ Congenital Cardiac Anesthesia Society: Winter Meeting Review

The 14th annual joint winter meeting of the Society for Pediatric Anesthesia (SPA) and the American Academy of Pediatrics (AAP) was held in Jacksonville, FL, in March 2009. The meeting began on Thursday, March 19, with the gathering of the Congenital Cardiac Anesthesia Society (CCAS) and a meeting of the Special Interest Group (SIG) for Pain Management in Children. The presentations at this meeting can be viewed in greater detail at the SPA website at <http://www.pedsanesthesia.org>.

CONGENITAL CARDIAC ANESTHESIA SOCIETY

The CCAS was formed in 2007 to support the advancement of highly specialized knowledge in the field of congenital cardiac anesthesia. Program chair Emad Mossad and the educational committee put together yet another excellent program. The meeting began with welcoming comments from CCAS president Dr. Chandra Ramamoorthy.

Dr. Mossad moderated the morning session "Heart Failure/Transplant." Dr. Jeff Towbin delivered an excellent review, "Cardiomyopathy in Children," which included the newly identified mitochondrial myopathies. He provided insight on the management of children with dilated, obstructive, and the less common but serious restrictive forms of cardiomyopathy. He emphasized that anesthesia providers should be aware of rhythm disturbances, the unique clinical variables associated with different forms of cardiomyopathy, and implications for anesthetics, cardiac medications, and intravascular volume expansion. Dr. Jack Copeland then spoke on ventricular assist devices (VADs) for children. He noted that 0.6%–6.8% of children undergoing cardiac surgery require postoperative mechanical support, most frequently extracorporeal membrane oxygenation (ECMO). The 1-yr survival in neonates awaiting transplantation on ECMO is 32% compared with 71% in those utilizing VADs as a bridge to transplant. Unfortunately, VADs cost about 3 times as much as ECMO. He concluded his talk with a discussion of the numerous improvements in the new VADs currently in development. These devices are expected to be fully implantable to allow for percutaneous insertion and provide uni- or biventricular assist possibilities with small prime volumes and a possible need for antiplatelet anticoagulation only. Dr. Barry Kussman then gave an overview entitled "Pediatric Heart Transplantation." He noted that although 350–400 pediatric heart transplants are performed each year, about 17% of recipients die while awaiting transplantation. He identified patient, donor, and institutional characteristics that affect mortality and emphasized the problems with coronary artery vasculopathy in survivors beyond 1 yr. He then reviewed the encouraging experience with ABO incompatible transplant in infants and discussed the growing list of "Failed Fontans" that await transplantation. A lively question and answer period followed. An excellent take-home point was made about the difficulty of providing effective cardiopulmonary resuscitation

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The 14th annual joint winter meeting of the Society for Pediatric Anesthesia (SPA) and the American Academy of Pediatrics (AAP) was held in Jacksonville, FL, in March 2009. The meeting began on Thursday, March 19, with the gathering of the Congenital Cardiac Anesthesia Society (CCAS) and a meeting of the Special Interest Group (SIG) for Pain Management in Children. The presentations at this meeting can be viewed in greater detail at the SPA website at <http://www.pedsanesthesia.org>.

CONGENITAL CARDIAC ANESTHESIA SOCIETY

The CCAS was formed in 2007 to support the advancement of highly specialized knowledge in the field of congenital cardiac anesthesia. Program chair Emad Mossad and the educational committee put together yet another excellent program. The meeting began with welcoming comments from CCAS president Dr. Chandra Ramamoorthy.

Dr. Mossad moderated the morning session "Heart Failure/Transplant." Dr. Jeff Towbin delivered an excellent review, "Cardiomyopathy in Children," which included the newly identified mitochondrial myopathies. He provided insight on the management of children with dilated, obstructive, and the less common but serious restrictive forms of cardiomyopathy. He emphasized that anesthesia providers should be aware of rhythm disturbances, the unique clinical variables associated with different forms of cardiomyopathy, and implications for anesthetics, cardiac medications, and intravascular volume expansion. Dr. Jack Copeland then spoke on ventricular assist devices (VADs) for children. He noted that 0.6%–6.8% of children undergoing cardiac surgery require postoperative mechanical support, most frequently extracorporeal membrane oxygenation (ECMO). The 1-yr survival in neonates awaiting transplantation on ECMO is 32% compared with 71% in those utilizing VADs as a bridge to transplant. Unfortunately, VADs cost about 3 times as much as ECMO. He concluded his talk with a discussion of the numerous improvements in the new VADs currently in development. These devices are expected to be fully implantable to allow for percutaneous insertion and provide uni- or biventricular assist possibilities with small prime volumes and a possible need for antiplatelet anticoagulation only. Dr. Barry Kussman then gave an overview entitled "Pediatric Heart Transplantation." He noted that although 350–400 pediatric heart transplants are performed each year, about 17% of recipients die while awaiting transplantation. He identified patient, donor, and institutional characteristics that affect mortality and emphasized the problems with coronary artery vasculopathy in survivors beyond 1 yr. He then reviewed the encouraging experience with ABO incompatible transplant in infants and discussed the growing list of "Failed Fontans" that await transplantation. A lively question and answer period followed. An excellent take-home point was made about the difficulty of providing effective cardiopulmonary resuscitation

in patients with Glenn or Fontan physiology and that ECMO should be considered before they arrest.

The next session, "Coagulation/Blood Transfusion," was moderated by Dr. Suanne Daves and began with a discussion by Dr. Nina Guzzetta entitled "Coagulation Monitoring in the OR and ICU." Dr. Guzzetta described the many causes of coagulopathy after cardiopulmonary bypass (CPB) in children and the need for adequate anticoagulation on CPB. She discussed the possible benefits of tailoring heparin doses using a heparin management system in addition to activated clotting time (ACT) (because it can be affected by factors other than heparin). She emphasized the utility of point-of-care activated whole blood tests of coagulation and suggested that coagulation parameters normalize better when cryoprecipitate rather than plasma is administered when bleeding persists despite platelet administration. Dr. Patricia Massicotte then presented her talk, "Transfusion Dilemmas in Pediatric Cardiac Surgery." She reviewed the types of blood products, the controversies surrounding leukoreduction, the necessity for irradiation, the age and type specificity of blood products, the use of directed donation, and infectious risks, especially cytomegalovirus (CMV). She identified the need for evidence-based data so that proper pediatric transfusion guidelines may be developed. In an excellent discussion entitled "Life After Aprotinin," Dr. Michael Eaton reviewed the use of lysine analogs ϵ -aminocaproic acid and tranexamic acid as antifibrinolytics. He discussed the use of strategies including "platelet anesthesia" or platelet inhibition during CPB with the use of epoprostenol and nitric oxide, combination therapy with heparin and direct thrombin inhibitors, and the concept of "biopassive" CPB circuits. Rescue therapy with recombinant activated factor VII has been found to decrease bleeding, but it has been associated with a significant risk of thrombosis. Dr. Eaton identified a need for randomized, prospective, multicenter trials of the most promising therapies directed at decreasing bleeding and need for transfusion.

The final morning session entitled "Hybrid Anesthesia—Myth and Reality" was moderated by Dr. James DiNardo. Dr. Helen Holtby discussed the benefits of the hybrid procedure, the set-up of the hybrid suite, and management of a single ventricle patient undergoing the hybrid procedure. She addressed timing of the atrial septectomy and the use of a "reverse"

Blalock-Taussig shunt to prevent coronary ischemia in the event of loss of retrograde flow to the ascending aorta. She reviewed the experience in Toronto from the past 5 yr. Drs. Pablo Motta and Peter Winch also shared their experiences at the Cleveland Clinic and at Nationwide Children's Hospital in Columbus. Although Dr. Motta felt that the hybrid offered no advantage over the Norwood, Dr. Winch was far more enthusiastic. Of 77 consecutive patients at Columbus, 60% were extubated at the end of the procedure, had an average intensive care unit stay of 5 days, and hospital stay of 12 days. He reported an interstage mortality of 14% and suggested that morbidity may be less than in the Norwood because of the ability to avoid CPB in the neonatal period.

The afternoon session of the CCAS began with a spirited panel discussion entitled "Who Should Provide Sedation/Anesthesia for Patients Undergoing Cardiac Catheterization?" moderated by Dr. Ramamoorthy. Dr. Laura Diaz presented convincing statistics to support her view that pediatric cardiac anesthesiologists are most suited for this task. Most patients are ASA physical status III and IV, at the extremes of age, and at high risk for cardiac arrest during the procedure. Dr. Ian James suggested that diagnostic catheterizations could be managed by the general anesthesiologist if they understood the hemodynamics, which way the blood flows, and the logistics of the cath suite. He argued that all pediatric anesthesiologists are trained to understand rhythm disturbances, to fear pulmonary hypertension (PHTN), and are able to treat these events. Dr. Jumbo Williams argued in favor of sedation by the cardiologist. He discussed practical issues such as the supply versus demand of pediatric general or cardiac anesthesiologists, as well as reimbursement and institutional support for anesthesiologist-directed sedation. Finally, he made the point that it is the cardiologist who best knows the physiology, the rhythms, the personnel, and procedures.

The next session was entitled "Electrophysiology Update." Cardiologist Dr. Naomi Kertesz offered important pearls and several practical tips in her presentation "Common Postoperative Arrhythmias and Their Management." The CCAS meeting concluded with a workshop entitled "Transesophageal Echocardiography in Children" moderated by Dr. Wanda Miller-Hance. After an informative overview of the basic transesophageal echocardiographic examination in patients with congenital heart disease by Dr. Miller-Hance, the

audience divided into 3 stations for individual workshops on different congenital heart lesions.

SIG ON PEDIATRIC PAIN

Another exciting new addition to the SPA educational program was the first meeting of the SIG on Pediatric Pain. This afternoon session chaired by Drs. Rita Agarwal and Sabine Kost-Byerly occurred concurrently with the CCAS and attracted more than 50 attendees.

Dr. David Polaner presented an update entitled "Pediatric Acute Pain Management." First, he discussed the ontogeny and development of pain responses in the neonate. He then discussed the use of parent- and nurse-controlled analgesia, which can be used safely within defined boundaries, and emphasized that a dose should never be delivered when the patient is asleep. He touched upon the use of small-dose naloxone infusions for treatment and prevention of opioid side effects and concluded with a discussion of ambulatory regional analgesia using continuous peripheral nerve blocks. Next, Dr. Steven Weisman presented "Perioperative Management of the Child with Chronic Pain." Patients receiving chronic opioid therapy may have tolerance and hyperalgesia. He emphasized the importance of continuing the patient's preoperative regimen, providing adequate opioid analgesia postoperatively, yet considering potential drug interactions. The nonsteroidal antiinflammatory drugs, selective serotonin reuptake inhibitors, and some anticonvulsants may cause increased bleeding. Many drugs used in these patients affect the metabolism of opioids, resulting in their accumulation. For patients receiving selective serotonin reuptake inhibitors that inhibit the 2D6 pathway, it is best to avoid drugs such as tramadol, codeine, and methadone. After surgery, psychotropic drugs should be restarted early. Regional techniques are beneficial, and adjunctive use of gabapentin should be considered.

Dr. Adrian Bosenberg presented "Regional Blockade for Postoperative Analgesia." He focused on ways to reduce the risk of regional blockade including the use of ultrasound to identify anatomic variants and optimal placement of the needle, and reduce the dose of drug necessary to achieve a successful block. He spoke about the fallacy that there is a threshold of current that is indicative of intraneural needle placement or of proper needle position. The best indicator of intraneural placement is resistance to injection greater than 20 psi. Ultrasound can compensate for anatomic variability and erroneous assumptions as to a

nerve's location based on inaccurate landmark data.

THE REGULAR SESSION OF THE WINTER MEETING OF THE SPA

The main session opened on Friday morning, March 20, with welcome messages from the Program Director, Dr. Linda Mason, Dr. Joseph Cravero, and SPA President Dr. Joseph Tobin. The SPA program then began with a session entitled *Controversies in Pediatric Anesthesia*. Dr. Carolyn Bannister kicked off the morning session with a talk entitled "Brain Function Monitoring in the Pediatric Patient—Where Are We Now?" In 2006, the ASA issued a practice advisory for intraoperative awareness and brain function monitoring in adults; however, there is little evidence on which to base a similar advisory in children. The reported incidence of awareness in children is approximately 1%, but studies are subjective and based on self-reporting. Brain function monitors provide an imprecise measure of the state of hypnosis and Dr. Bannister cautioned against their use in infants because of maturational differences in the electroencephalogram. A strong correlation has been found between anesthetic levels and bispectral index values in children older than 6 mo. Narcotrend and Entropy monitors have been validated in children older than 12 mo. Pediatric studies of the Cerebral State Monitor are lacking, and the auditory-evoked potential monitor poorly predicted end-tidal anesthetic concentrations in infants and children. Pediatric anesthesiologists should take an active role in testing algorithms upon which such monitors can be developed for use in children.

Dr. Randall Flick then presented "Clinical Perspectives in Anesthetic Toxicity." Although it is known that early exposure to some anesthetics and sedatives causes neurohistopathologic and behavioral changes in rodents, extrapolation of these findings to humans is questionable. Dr. Flick presented the findings of a study that evaluated the association between early exposure to anesthesia and learning disability (LD) in 8458 children who required general anesthesia before their fifth birthday.¹ Educational records and records of the only private tutoring agency in the community were reviewed. In the final sample of 5357 children, the risk for developing a LD increased with the number of anesthetics before the age of 4 yr ($P < 0.001$). Although children exposed to a single anesthetic were not at increased risk, those exposed to 2 or more anesthetics or those who received anesthesia for a longer duration were at

increased risk of LD. Dr. Flick noted that based on these data, it is not possible to conclude whether exposure to anesthetics was causative for LD or rather a marker for conditions that increase LD risk.

The second morning session entitled "Emerging Technologies and Techniques for Pediatric Patients" was moderated by Dr. Lynne Maxwell. Dr. John Arnold reviewed modes of ventilating children with acute lung injury in his lecture entitled "New Modes of Mechanical Ventilation for Children." He discussed high-frequency oscillation ventilation, which allows for bulk delivery of oxygen and effective recruitment of alveoli, while delivering minimal tidal volumes at high rates. Next, Dr. Arnold described airway pressure release ventilation whereby patients breathe spontaneously with continuous positive airway pressure to maintain airway recruitment. He went on to explain the concept of neurally adjusted ventilatory assistance that uses a computer-assisted analysis of electrical diaphragmatic activity to adjust ventilation, both within a breath and between breaths. Data provided from the electrical diaphragmatic activity signal are used to improve synchrony between the patient and the ventilator and to facilitate weaning.

The next speaker, Dr. Ivor Berkowitz, presented "Uses of Cardiac Support Outside the OR." Dr. Berkowitz began with a discussion of ECMO, its indications, and the differentiation of VA ECMO versus ECMO as a left or right VAD. He also spoke about the usefulness of ECMO in cardiac failure, but discouraged its use when recovery is not viable. He discussed various approaches for cannulation and potential complications. Next, Dr. Berkowitz discussed ECMO in the context of extracorporeal cardiopulmonary resuscitation including indications, decision-making processes, and delivery systems. Percutaneous cannulation is preferred, and speed is of the essence. He ended with a discussion of VADs including the Berlin Heart and the Medos VAD.

Dr. Jay Deshpande moderated the last session of the morning entitled "New Drugs on the Horizon for Pediatric Anesthesia." Dr. Greg Hammer presented "Intravenous Acetaminophen," which is widely used in Europe but yet to be approved in the United States. The benefits of IV acetaminophen include its efficacy as an analgesic and antipyretic and its wide therapeutic index with a safety profile comparable to the oral form. IV administration yields target therapeutic concentrations of 10–20 $\mu\text{g}/\text{mL}$ in 15 min to 2 h. The rate of hepatic clearance increases up to

age 2 yr when it approaches that of adults. Despite its delayed clearance in neonates, there is no increase of serum transaminases. Hepatotoxicity does not occur because neonates have an increased ability to metabolize IV acetaminophen via the sulfate pathway and rarely utilize the oxidative pathway, therefore metabolites toxic to the liver are not produced.

Dr. Nina Guzzetta followed with a talk called "Recombinant Factor VII (rVIIa)." rVIIa is approved by the Food and Drug Administration (FDA) for the treatment and prevention of bleeding in patients with hemophilia A and B with antibodies to factors VIII and IX or in those with factor VII deficiency. Off-label uses include bleeding associated with nonhemolytic conditions, such as liver failure or transplantation, intracerebral hemorrhage, postoperative hemorrhage, or postbypass coagulopathy. Findings from observational studies of a temporal relationship between use of rVIIa and decrease in blood loss were not substantiated by randomized controlled trials. Adult studies/case reports reveal that the use of rVII is more effective when administered early, before the occurrence of severe bleeding. Adult dosing varies from 40 to 90 $\mu\text{g}/\text{kg}$. The upper end of this range is required in children because of the shorter half-life and more rapid clearance of rVIIa. Disadvantages include the high cost, lack of an assay to predict its efficacy, unknown safety profile, and thromboembolic complications. Because a reduction in antithrombin enhances the hemostatic effects of the drug, specific monitoring of antithrombin levels may limit the incidence of complications. Randomized trials are needed to assess its efficacy and safety.

In his talk on the investigational reversal drug sugammadex, Dr. Jay Deshpande reviewed its structure stating that its negatively charged side chains bind to the positively charged side ions of rocuronium and vecuronium resulting in a tightly bound moiety that is excreted in urine whereas the inactive, uncomplexed drug is excreted in bile. Although sugammadex does not bind with benzylisoquinoline agents or succinylcholine, it forms complexes with other medications such as cortisone, atropine, and verapamil albeit with much less affinity and therefore does not result in significant clinical effects. The amount of sugammadex required is proportional to the amount of neuromuscular agent administered, and side effects are infrequent. Plaud et al.² reported 90% recovery of T4 in all pediatric age groups after its administration. Although this is a promising drug with a good safety profile, it has

not yet been approved by the FDA because of reports of hypersensitivity reactions. Another concern will be its expected high cost compared with generic reversal drugs.

Dr. Constance Monitto discussed the peripheral opioid antagonists methylnaltrexone and alvimopan, which have recently received FDA approval. Neither cross the blood-brain barrier and therefore function only as peripheral antagonists at opioid receptors. Alvimopan is administered orally whereas methylnaltrexone can also be administered via the IV or subcutaneous routes. Methylnaltrexone is approved only for the treatment of opioid-induced constipation in patients receiving palliative care or long-term illness, and its gastrointestinal side effects contraindicate its use in mechanical gastrointestinal obstruction. Pediatric studies are lacking on the use of this drug.

The afternoon session comprised a series of workshops and refresher courses. These sessions were followed by a lively, educational, and entertaining session of Jeopardy moderated by Dr. Frank McGowan. This session allowed for audience participation and generated a stimulating discussion of several practical issues related to the perioperative care of children.

Saturday, March 21 started with a variety of early morning problem based learning discussions (PBLDs) followed by the first morning session entitled "Pulmonary Core" moderated by Dr. Mary Ellen McCann. Dr. Walter Robinson identified cystic fibrosis (CF) as a chronic disease with long-term implications, but with aggressive management, disease exacerbations occur later in life. Patients with CF may be taking many medications and alternative remedies so that drug interactions must be considered, for example, hypertension associated with licorice and bleeding complications with ginkgo biloba. Comorbidities such as diabetes may be unmasked by the stress of surgery. Respiratory isolation may be required in patients infected with drug-resistant bacteria and fever may be a grave sign of impending sepsis. Nasal intubation should be avoided because nasal polyps and sinus diseases may be present. Increased mucus production may result in hypoxemia.

Dr. Gerhard Wolf then discussed asthma, the third leading cause for hospital admission in children in the United States. Dr. Wolf identified therapies with little to no effectiveness in asthma including ipratropium, theophylline, antibiotics, hydration, chest physiotherapy, mucolytics, and sedation. Goals for mechanical ventilation, when required, include smaller tidal

volumes, decreased inspiratory time, permissive hypercapnia, nontoxic oxygen concentration, and use of expiratory hold maneuvers. Positive end-expiratory pressure reduces the work of breathing by preventing end-expiratory alveolar collapse. Data regarding the benefits of Heliox in preventing intubation in asthmatics are unconvincing. Isoflurane and IV magnesium may be useful when standard measures fail.

The last speaker of the session, Dr. Brian Hanna, presented "Pulmonary Hypertension" (in children). The incidence of PHTN is 1–2 per million, yet cor pulmonale is responsible for 20% of mortality in the neonatal intensive care unit. Perioperative mortality in patients with PHTN is 1%–2% with increased right ventricular pressure posing the greatest risk for mortality. Three main etiologies for PHTN in children include abnormal lung development, supernumerary vessels in abnormally developed lung tissues or intimal hyperplasia, and arteriopathy in the pulmonary vasculature. Elevation of serum β -natriuretic peptide has been shown to correlate with increased mortality. Research on treating these patients is geared toward inducing apoptosis in proliferated smooth muscles to limit further proliferation and improving angiogenesis.

The AAP Section on Anesthesiology and Pain Medicine "Ask the Experts" Panel presented "Anesthesia for Children with Pulmonary Disease," which was sponsored by Nemours Children's Clinic of Jacksonville and Monroe Carell Jr. Children's Hospital at Vanderbilt. Dr. Eugene Freid tackled the first case of a 3 yr old with PHTN controlled with a prostaglandin, endothelin-1 inhibitor, and phosphodiesterase inhibitor who required exchange of her central line through which she was receiving epoprostenol (Flolan). A recent review showed that PHTN is a direct predictor of perioperative mortality. To decrease perioperative morbidity, current cardiac studies reflecting the reversibility of PHTN with oxygen and vasodilators are essential. Maintenance of physiologic balance and prevention of hypoxia, acidosis, and sympathetic stimulation are imperative to minimize elevations in pulmonary pressures. Effective treatment of a PHTN crisis includes oxygen, hyperventilation, intravascular volume expansion and cardiac support (with milrinone as the first line drug), avoidance of noxious stimuli, and inhaled nitric oxide.

Dr. Kevin Sullivan took on the challenge of an obese 14 yr old with chronic persistent asthma treated with montelukast, inhaled fluticasone, and albuterol undergoing slipped capital femoral

epiphysis repair. He discussed the value of a comprehensive preoperative history and recommended the use of IV steroids and inhaled β -agonists before induction in such patients. A deep plane of anesthesia should be achieved, and IV lidocaine administered before instrumentation of the airway. Histamine-releasing drugs should be avoided. Awake extubation is a viable option and airway reactivity could be lessened by the use of a bronchodilator and potentially a dose of dexmedetomidine at the end of surgery. He emphasized the use of β -agonists, magnesium sulfate, and additional IV steroids if intraoperative bronchospasm develops. Ventilator management should include sufficient time for exhalation (respiratory rates of 4–10/min), low tidal volumes (4–7 mL/kg), and no positive end-expiratory pressure. He cautioned the audience that hypercapnia has minimal sequelae compared with the significant morbidity caused by barotrauma.

Dr. Stephen Hays described his approach to the last case of a child with CF undergoing flexible bronchoscopy for lower lobe atelectasis. Recent studies suggest that airway management with a laryngeal mask airway is safe, well tolerated, and has minimal respiratory complications in patients with CF. Respiratory deterioration is common in children after bronchoscopy and bronchoalveolar lavage but is usually transient and well tolerated. He recommended that if there is a potential long-term benefit from the proposed procedure, proceeding with surgery is probably indicated despite poor underlying respiratory function, with the understanding that initial postoperative respiratory deterioration is expected, treatable, and in most cases short term. A variety of workshops were available to participants on both Friday and Saturday afternoons (Table 1).

The Winter SPA Sunday Sessions began with another morning of PBLDs and a breakfast discussion. Dr. Debra A. Schwinn gave the SonoSite Lecture entitled "Genetics and Anesthesiology: Defining the Vulnerable Patient." She discussed the role that ongoing genomic revolution may play in the development of patient-focused drug therapy and our ability to improve patient care. The role of genome-based medicine will be to identify genetic factors that patients possess that may either protect them or create problems when they undergo anesthesia or surgery. These differences occur at many levels: changes in DNA code (pharmacogenomics), differences in RNA expression (the transcriptome), differences in protein expression (the proteome), and alterations in metabolic

Table 1. Workshops

| Title | Speakers |
|---|---|
| Fellows research workshop | Alan Tait, PhD |
| Junior faculty workshop—success in academics | Samuel David Yanofsky, MD, MSED Franklin Cladis, MD; Ira Cohen, MD; Divya Dixit, MD; Julie Nyquist, PhD; Joseph Tobin, MD, FAAP; Mary Lou Voytko, PhD |
| Epidural placement in children, infants, and neonates | Christine Greco, MD, FAAP Jeffrey Koh, MD; Benjamin Lee, MD, MPH; Navil Sethna, MB, ChB |
| Peripheral nerve block | Edward Rivera Mariano, MD Jeffrey Steinfeldt, MD; Andreas Taenzer, MD; FAAP |
| New devices and new approaches to the pediatric airway | David Polaner, MD, FAAP Jeffrey Galinkin, MD, FAAP; Cheryl Gooden, MD, FAAP; Geoffrey Lane, MB, BCh; Bruno Marciniak, MD; Peter Szmuk, MD |
| Dexmedetomidine: clinical applications and limitations | Keira Mason, MD Julia Finkel, MD; Gregory Hammer, MD; Constantinos Chrysostomou, MD, FAAP |
| Techniques for difficult peripheral access | Gregory Schears, MD Darryl Berkowitz, MB, BCh; Dawit Haile, MD; Scott Markowitz, MD; Luis Zabala, MD |
| Practical approaches to quality improvement in anesthesia | Donald Tyler, MD, MBA Sean Flack, MB, ChB, FRCA; Ari Weintraub, MD; Anna Mary Varughese, MD, MPH |
| Personal financial planning, 2009 | Jonathan Griswold, MD |
| Epidural analgesia for children | John Rose, MD, FAAP Julia Finkel, MD; Kenneth Goldschneider, MD, FAAP; F. Wickham Kraemer, III, MD |
| Advanced ultrasound-guided regional workshop | Edward Rivera Mariano, MD Jeffrey Steinfeldt, MD; Andreas Taenzer, MD, FAAP |
| Integrating acupuncture in pediatric perioperative care and pain medicine | Yuan-Chi Lin, MD Brenda Golianu, MD; Rosalie Tassone, MD; Shu-Ming Wang, MD |
| Simulation in pediatric anesthesia | Anita Honkanen, MD Richard Blum, MD, MSE, FAAP; Michael Chen, MD; Rebecca Claire, MD; Harshad Gurnaney, MD; Aruna Nathan, MBBS; Andreas Navedo-Rivera, MD; Sharon Redd, MD; Ellen Wang, MD; Radhamangalam Ramamurthi, MD, FRCA |
| Teaching the advanced ACGME competencies | Samuel David Yanofsky, MD, MSED Ira Todd Cohen, MD; Barry Markovitz, MD, MPH; William McIlvaine, MD, CM, FRCPC; Niurka Rivero, MD; Julie Nyquist, PhD; Randall Wetzell, MBBS, FAAP |

pathways. These pathways can be studied using biochemical techniques that are currently making their way from the bench to the bedside. Dr. Schwinn mentioned an upcoming meeting at the National Institutes of Health to discuss the development of pediatric studies, some of which should involve assessing the effects of different genetic factors on perioperative outcomes in children.

After the breakfast discussion, an interesting morning that focused on journals and publications ensued. Dr. Peter Davis gave the audience important pearls in his presentation entitled "What a Reviewer Wants to See in a Manuscript" and "What an Editor Wants to See in a Manuscript." Next, the 2008 Editors' Best Picks for 3 journals were presented by Dr. Peter Davis for *Anesthesia & Analgesia*, Dr. Zeev Kain for *Anesthesiology*, and Dr. Robert Friesen for *Pediatric Anesthesia*. After the moderator's pick by Dr. Charles Coté and a discussion period, the SPA Winter Meeting was adjourned. One of the

highlights of the SPA meeting in Jacksonville was the presentation of the Robert M. Smith Award to Dr. Frederic Berry and Dr. D. Ryan Cook for their outstanding achievements in the field of pediatric anesthesia.

FUNDAMENTALS OF PEDIATRIC ANESTHESIOLOGY

New to the SPA family of conferences was "Fundamentals of Pediatric Anesthesiology," a course designed to meet the needs of general anesthesia practitioners who care for children in the community hospital. The program organized by Drs. Randall Flick, Paul Samuels, Nancy Glass, and Lynn Martin included a wide breadth of topics relevant to the everyday practice of pediatric anesthesia in this setting. The goals of the meeting were to provide the attendees with the core knowledge required to provide care to children undergoing routine procedures. Because it was held concurrently with the

SPA/AAP winter meeting, it allowed registrants of the Fundamentals course to attend the workshops and refresher courses offered at the SPA meeting.

The morning session on Friday was moderated by Dr. Rita Agarwal. Dr. Shobha Malviya opened the morning session with a comprehensive overview entitled "Preoperative Evaluation and Common Co-Existing Diseases in Children," which includes asthma, heart murmurs, prematurity, and upper respiratory infections. This was followed by an in-depth review entitled "Pre-medication and Anesthetic Induction" by Dr. Peter Davis. Dr. Lynn Martin moderated the second session, which began with an excellent discussion on fluid, electrolyte, and glucose management by Dr. Frederic Berry. Next, Dr. Nancy Glass discussed the pitfalls of anesthetizing children for tonsillectomy and the many adverse events that can occur during and after this procedure. The program on Friday concluded with an "Ask the Experts" panel discussion.

The experts included Drs. Steve Hall, Allison Kinder Ross, and Randall Clark.

On Saturday, the Fundamentals program began with a breakfast panel on postanesthesia care unit (PACU) issues, including nausea and vomiting, emergence delirium, and management of persistent pain, discussed by Drs. Cathleen Lammers, Constance Houck, and Ira Landsman. These issues arise several times each day in the PACU and as such have tremendous relevance to the care of anesthetized children particularly in settings that care for both adults and children. In the next session, Dr. Adrian Bosenberg presented "Pediatric Regional Techniques Suitable for Community Practice" and offered several practical tips that can be applied to their use. The next speaker, Dr. Thomas Cox talked about emergencies in pediatric anesthesia including foreign bodies in the airway or esophagus, bleeding tonsil, and neonatal emergencies such as pyloric stenosis and incarcerated inguinal hernia. Dr. Richard Kaplan then presented "Anesthesia and Sedation Outside the Operating Room" followed by Dr. Lynne Maxwell who offered several insights into the management of the difficult pediatric airway. The program concluded with a short overview of hot topics related to

the practice of pediatric anesthesia. These included "Anesthetic Neurotoxicity" by Dr. Sulpicio Soriano, "Use of BIS Monitoring in Children" by Dr. Frank McGowan, "Dexmedetomidine" by Dr. Joseph Cravero, and "Malignant Hyperthermia" by Dr. Barbara Brandom.

The Fundamentals course attracted approximately 50 attendees. The lectures were well received and the speakers uniformly received excellent evaluations from the audience. Plans are currently underway for this program to be held in conjunction with the 2010 SPA/AAP winter meeting in San Antonio. In addition to continuing medical education credits, the course will offer nursing credits for the benefit of nurse anesthetists and PACU nurses who may also benefit from the expertise of the speakers.

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