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Fibrin Sealant in Operative Medicine

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Preface

Fibrin plays a prominent role in wound healing. It has a hemostatic effect, induces cellular response to wound damage, and, by forming strands to build a matrix, assists in neovascularization and fibroblast proliferation.

The concept of using clotting substances from human blood for wound management and to achieve hemostasis in bleeding parenchymatous organs can be traced to 1909, when Bergel [1] reported on the hemostatic effect of fibrin powder. In 1915, Grey [3] employed fibrin to control bleeding in neurosurgical operations of the brain. A year later, Harvey [4] used fibrin patches to stop bleeding from parenchymatous organs in general surgery.

It took more than two decades for this ingenious idea to be rediscovered. In 1940, Young and Medawar [8] reported on experimental nerve anastomosis by sealing. Similarly, Tarlov and Benjamin [7] reunited nerves with plasma clots in 1943. Tarlov improved the results obtained with clot anastomosing of nerves by avoiding tension at the nerve stumps. In 1944, Cronkite et al. [2] reported on an initial series of eight cases in which fibrinogen and thrombin had been used successfully for anchoring skin grafts.

Although these early attempts suggested the basic advantages of using a biomaterial for wound closure – such as complete absorption, improved wound healing, and excellent tissue tolerance – the failure rate was relatively high, mainly because the fibrinogen employed had poor adhesive strength and the sealing did not last. It was because of these unsatisfactory results that the technique was not further pursued in the decades to follow.

In 1972, the use of fibrin as a biologic adhesive was revived by Matras et al. [6], who successfully employed a fibrinogen cryoprecipitate for reuniting peripheral nerves in an animal model. Matras and Kuderna used autologous material in the first successful human application in 1975 [5]. It was not until a special cryoprecipitation process had been developed that it was possible to produce a highly concentrated fibrinogen solution with an enriched factor XIII content, as the basis of two-component fibrin sealant.

In the meantime, the controversial issue of virus transmission, including the transmission of HTLV-III, by the blood product Tisseel (Tissucol) has been resolved. In addition to subjecting Tisseel (Tissucol) to in-process virus inactivation, both the source material and final product are routinely screened for HTLV-III antibody.

Following the first international symposium on fibrin sealant in Vienna in 1985, which dealt with the use of the product in various surgical disciplines, this seven-

volume study attempts to present current knowledge relating to the method of fibrin sealing. The disciplines covered are: general and abdominal surgery; ophthalmology and neurosurgery; otorhinolaryngology; plastic, maxillofacial and dental surgery; thoracic and cardiovascular surgery; traumatology and orthopaedics; urology, gynaecology and obstetrics. Each volume is preceded by a general chapter on the principles of fibrin sealing, methods of application, aspects of quality control, and safety studies.

Today, fibrin sealing has become an accepted tool in many fields of surgery. In many areas, fibrin sealing has superseded conventional surgical techniques, increased postoperative safety, and even made new therapeutic approaches possible.

We would like to thank all authors for their excellent contributions and helpful photographs, which have made these seven volumes on fibrin sealing possible.

Vienna, Juni 1986

G. Schlag
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I. Principles of Fibrin Sealing

The Importance of Fibrin in Wound Repair

G. SCHLAG, H. REDL, M. TURNHER, and H.P. DINGES

Key words: wound healing, fibrin, macrophages, granulocytes

Abstract

A review is given, beginning with the inflammatory phase of wound healing and explaining the role of macrophages, platelets, and granulocytes. Beside the cellular response the special importance of fibrin and factor XIII is demonstrated, particularly their function for fibroplasia. Special emphasis is put on the effect of highly concentrated fibrin – fibrin sealant. Its beneficial role in promoting the growth of fibroblasts is shown by a study on rats, in which a new model of granulation tissue formation was used. With this model it can be demonstrated that the application of fibrin sealant leads to significantly higher amounts of fibroblasts in newly formed granulation tissue. However, it is also demonstrated that fibrin sealant cannot overcome the inhibition of wound healing caused by, for example, adriamycin, though the beneficial effect of fibrin sealant in other cases of disturbed wound healing, e.g., ulcus cruris, has been demonstrated previously.

General Aspects

Three phases of wound healing are seen following trauma:
- Inflammatory phase
- Fibroplasia
- Protective maturation phase

Tissue trauma is immediately followed by coagulation and hemostasis. Coagulation eventually leads to conversion of fibrinogen into fibrin via the humoral pathway under the influence of thrombin and calcium (Fig. 1).

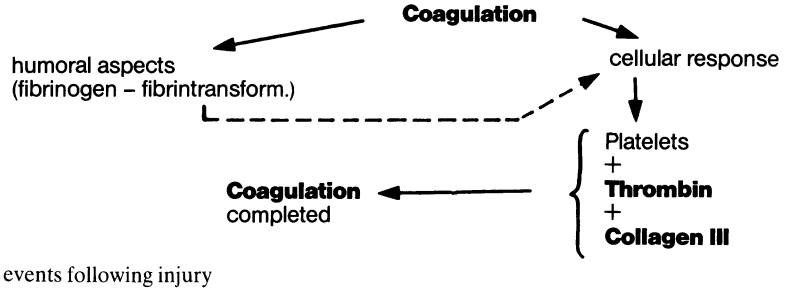

Fig. 1. Primary events following injury

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During the coagulation process, a cellular response is seen. Together with thrombin and collagen III, the platelets complete coagulation. Adhesion of the platelets to collagen fibrils of type III [3, 20] leads to platelet aggregation, where the platelets change from a reversible into an irreversible form. 5-Hydroxy-tryptamine and epinephrine are released from the platelets, which undergo further aggregation. Other substances are released from platelets, like platelet factor III, which acts on the formation of thrombin. Platelets are also important for the fibrin network structure, since they make fibrin more resistant to mechanical shear forces and to fibrinolysis [13].

The coagulation activated via humoral as well as cellular pathways leads to the blood clot which acts as a sealant primarily because of its fibrin content. In this way, normal hemostatic mechanisms help to prevent contamination and loss of body fluids as well as providing a substrate material for cell growth [2].

Fibrin is essential since it causes chemotaxis [24] of PMNs (in vitro) in the presence of fibrin degradation products. Fibrin mainly leads to recruitment in the injured tissue and also activates the macrophages.

Immediately after trauma and the ensuing coagulation, the inflammatory phase (lag phase) starts and extends to the 4th or 5th day. This phase is a vital part of the wound repair process. The local neutrophils (PMNs) increase within several hours. The main task of PMNs is to degradate damaged tissue (debriding) and to phagocytose cell debris. The migration of PMNs is presumably caused by chemotactic substances released from aggregated platelets or from plasma components (proteases, fibrinopeptide A). During the first 48 h the PMNs increase markedly and are quickly subject to lysis. Only a few are engaged in phagocytosis [22]. Evidence from studies using antineutrophil serum suggests that the PMNs are not essential in normal wound healing.

After some days, the most important cellular components in the inflammatory phase, i.e., the "monocytes", migrate (Fig. 2), change into macrophages, and reach their maximum number in the wound between the 4th and 5th day. The macrophages serve many different functions. According to Gustafson [15], these include regulation of coagulation (macrophage-induced procoagulant activity, factors V, VII, IX, and X) and fibrinolysis; elimination of cells, tissue debris, and bacteria; and regulation of fibroblast activity (fibroblast growth factor). Their main tasks include

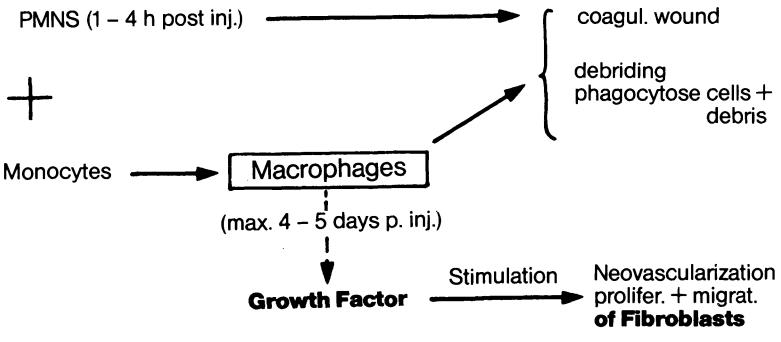

Fig. 2. Inflammatory phase of wound healing

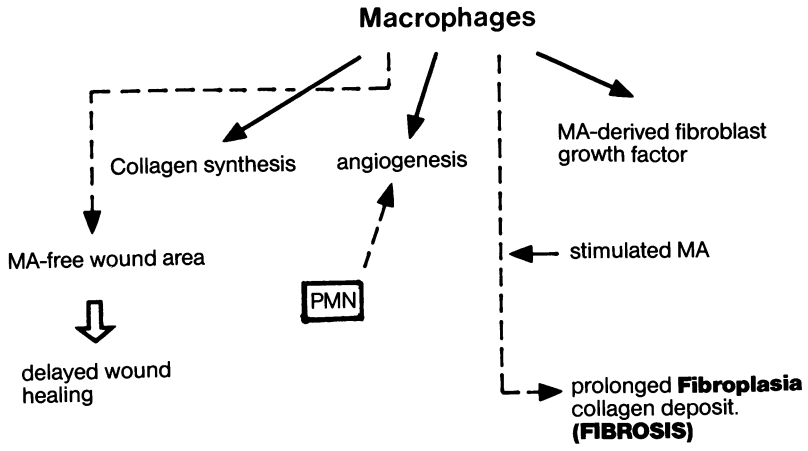

Fig. 3. The role of macrophages during the inflammatory phase of wound healing

phagocytosis of fibrin and the release of growth factors which stimulate fibroblast and endothelial cell proliferation in vitro [14, 28]. Induction of angiogenesis by wound macrophages has been confirmed [12, 21] (Fig. 3). Hunt et al [21] reported that this activity involved macrophages more than PMNs; however, a granulocyte component in the production of angiogenesis could not be excluded. Macrophages are responsible not only for neovascularization in the wound but also for stimulation of collagen synthesis. Collagen synthesis requires fibroplasia. Here, the "macrophage-derived fibroplast growth factor" apparently plays a vital part. If antimacrophage serum is administered, wound healing is severely delayed. On the other hand, prolonged activation of macrophages (endotoxin, bacterial products) may result in exaggerated fibroplasia and collagen deposition, which ends in fibrosis [21].

As to the cellular response in wound healing, the platelets in connection with fibrin play an important part [25]. Activated by thrombin, the platelets release a mitogen for fibroblasts and smooth muscle cells and stimulate collagen synthesis. This mitogen was isolated as "platelet-derived growth factor".

Fibroplasia and collagen synthesis start within 24 h following trauma. The platelets also activate neovascularization. Thus vital factors for wound healing are released by the platelets, which are largely responsible for the healing process (Fig. 4).

Wound healing is influenced by local oxygenation. Banda et al. [4] have shown that anoxia leads to stimulation and activation of the macrophages. This causes production of an angiogenesis factor and a macrophage-derived growth factor which stimulates the fibroblasts.

Knighton et al. [26] have demonstrated hypoxic stimulation of angiogenesis by macrophages in a corneal assay. Hyperoxia appears to suppress angiogenesis as shown in a second experiment with an ear chamber equipped with oxygen-perme-

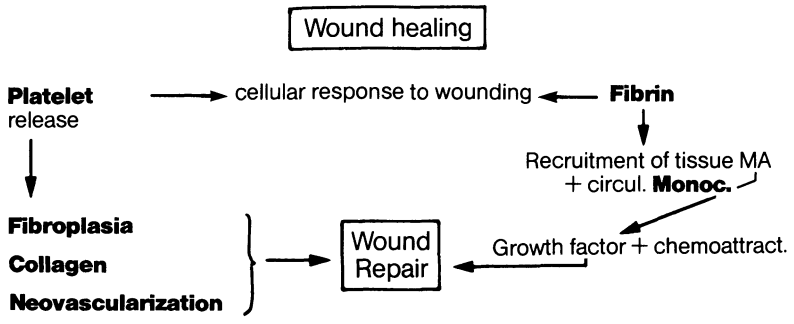

Fig. 4. The concert action of fibrin and platelets

able or -impermeable membranes. The demonstration that respiratory oxygen concentration affects the tensile strength of healing wounds and granulomas may reflect macrophage regulation of angiogenesis or fibroplasia [31, 32].

Granulation tissue plays a key role in the healing of all organs, except for those of epithelial origin. Granulation tissue largely consists of macrophages, endothelial cells, and fibroblasts [36]. The hallmark of granulation tissue is the proliferative response of fibroblasts. Proliferation is stimulated by a substance produced by macrophages (growth factor). It is thus very important that the cellular phase (inflammatory phase) is not influenced as to the quality and quantity of the cells. Macrophages are a crucial component of the initial inflammatory reaction which precedes fibroplasia. The administration of corticosteroids in experimental conditions results in significantly fewer monocytes and macrophages in the cellular infiltrate. The effect of fewer macrophages is that the accumulation of collagen – measured as hydroxyproline content – is decreased and neovascularization is inhibited [38].

Fibroblasts proliferate within the first 3 days after trauma. In connection with neovascularization, fibroblasts become the dominating cells in collagen and proteoglycans synthesis. Collagen is also lysed throughout wound repair, perhaps due to fibroblasts. Fibroblasts are responsible for the synthesis of glycosaminglycans, which surrounds the collagen network and absorbs the compressive load as a hydrated viscous gel [27, 30].

Specific Effects of Fibrin, Thrombin, and Factor XIII

Fibrin is vital in wound healing since the network formed in the wound acts both as a scaffold for migrating fibroblasts and as a hemostatic barrier [33]. This scaffold is formed by fibrin strands in connection with fibronectin. In large quantities, fibrin has an inhibitory effect on cell migration and may even delay wound healing. Fibroblasts are quickly followed by new capillaries. These are essential for the granulation tissue. The endothelial cells contain plasminogen activator, the subst-

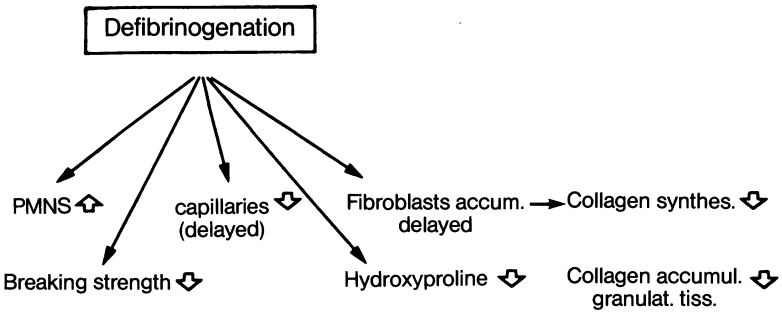

Fig. 5. Effect of defibrinogenation on the different aspects of wound healing

ance that initiates the process of fibrin removal (fibrinolysis). Banerjee and Glynn [5] have demonstrated that implanted fibrin clots are invaded by new capillaries and fibroblasts.

The importance of fibrin in wound repair was confirmed by Brändstedt et al. [7–11]. Defibrinogenation with! Arvin has been used in studies on the formation of granulation tissue (Fig. 5). Under these conditions the fibrin strands are irregular and disrupted, and the number of fibroblasts and collagen fibrils is reduced. As a result of this, a reduction of collagen accumulation in the granulation tissue has been observed. Controlled fibrin deposition appears necessary for granulation tissue formation and for normal healing.

Deposited fibrin apparently stimulates the formation of granulation tissue, including increased collagen precipitation [17]. Hydroxyproline directly reflects the collagen concentration and was significantly high in a fibrin-filled Teflon implanted cylinder [16]. Pohl et al. [34] confirmed the influence of fibrin on growing fibroblasts in vitro by showing that fibrin markedly enhances cellular growth as well as mitosis of the fibroblasts. After 10 days, the cell growth stops. The network of fibrin fibers promotes growth and multiplication of the fibroblasts. As long ago as 1960, Banerjee and Glynn [5] demonstrated that implanted fibrin clots are invaded by new capillaries and fibroblasts.

Thrombin has mitogenic characteristics in cell cultures, aside from its effects on platelet activation, such as long-lasting hormone-like influence on fibroblast proliferation [34], on transformation of factor XIII to XIIIa, on conversion of fibrinogen to fibrin, on prostaglandin production, and on activation of protein C [15]. The effect of thrombin in wound healing is manifold and is a vital part of wound repair.

Factor XIII is needed in the cross-linkage of fibrin in order to produce a stable fibrin network which provides the matrix for the ingrowing fibroblasts. The delay in wound healing in factor XIII-deficient patients may be due to lack of stimulation of fibroblast proliferation [23]. The attachment of fibroblasts is not only obtained by the fibrin matrix, but also (indeed, mainly), through the cross-linkage by activated factor XIII. Cross-linkage between fibrin fibers promotes the cellular response and thus subsequent migration and proliferation of fibroblasts. Factor XIII is also cross-linked with collagen, fibronectin, and α^2-antiplasmin [29].

Fibrin Sealant

For more than 10 years, fibrin sealant (Tissucol/Tisseel), a two-component sealant, has been widely used in surgical medicine and its disciplines.

Tissucol has a triple effect on wound healing. Due to its hemostatic effect, hematoma formation is avoided; consequently the lengthy process of absorption and possible organization of the hematoma does not take place and the rather negative influence of the hematoma on the quality of the granulation tissue is also avoided.

As far as the adhesive effect of Tissucol is concerned, critics have repeatedly pointed out its limited adhesive strength, which will not tolerate major stress exposure. It should, however, be remembered that the objective of using fibrin sealant is not confined to sealing severed tissue segments. Proper adaptation of dissociated surfaces is just as important because it ensures smooth wound healing unhampered by an artificial barrier such as is introduced with synthetic sealants.

The third effect of a fibrin sealant, at least as far as Tissucol/Tisseel is concerned, is on the physiological network structure [35]. This fibrin network is an excellent substrate for the ingrowth of fibroblasts, which will be demonstrated in the study below.

Materials and Methods

To determine the effect of Tissucol on the formation of granulation tissue we developed a spongiosa-based granulation tissue model. The model uses blocks of lyophilized Kieler spongiosa. They were decalcified with hydrochlorous acid and fixed with glutaraldehyde to cross-link the collagen structure. The blocks were then subcutaneously implanted into rats. The cavities of the spongiosa were either filled with a substance that influenced local wound healing, e.g., homologous fibrin sealant, or left empty for controls. The spongiosa blocks were removed at certain time intervals. The granulation tissue was biochemically examined after proteolytic removal from the spongiosa, e.g., to determine the DNA and hydroxyproline content. On the other hand, the granulation tissue was morphometrically evaluated following fixation and prepared for electron microscopy using standard techniques. The space filled by granulation tissue within a given time was precisely determined and the composition of the granulation tissue evaluated. With these methods, we determined the quantity of granulation tissue and the cellular (fibroblasts, capillaries) and biochemical (hydroxyproline, DNA) composition. This model seems very useful since no foreign body reaction was seen, in contrast to the reaction frequently observed after cellular sponge implantation according to Hølund [19].

A total of 72 male Wistar rats were distributed into four equally sized groups. The animals were given intramuscular anesthesia with Ketalar-Rompun, and some of them then received adriamycin (6 mg/kg body weight) before implantation of the spongiosa blocks. All animals underwent paravertebral implantation of two sterile spongiosa blocks with or without fibrin sealant under the dorsal skin. The four groups were thus as follows:

Groups O (F + A): Implantation of spongiosa blocks soaked with fibrin sealant with systemic application of adriamycin.

Group 1 (F): Implantation of spongiosa blocks soaked with fibrin sealant without systemic application of adriamycin.

Group 2 (A): Implantation of spongiosa blocks with systemic application of adriamycin, without fibrin sealant.

Group 3 (CO): Implantation of spongiosa blocks without further systemic or local treatment (control group).

The animals were killed on the 7th or 14th postoperative day.

Results and Discussion

We found a significant fibroblast-stimulating effect of the sealant (16% fibroblasts per volume granulation tissue in controls, 22% in the fibrin sealant group without adriamycin). As opposed to this, the inhibitory effect of the cytostatic agent adriamycin on the formation of granulation tissue was not improved by the sealant (11% without and 10% with sealant). As a cytotoxic chemotherapeutic drug, adriamycin inhibits wound repair. It causes inflammatory arrest, suppresses protein synthesis, and inhibits cell replication [6].

On the electron micrograph, immature (undifferentiated) cells were seen in the adriamycin group (Fig. 6). After 7 days, fibrin strands were markedly visible (Fig. 7), as against the pure fibrin sealant group, in which the fibrin was largely

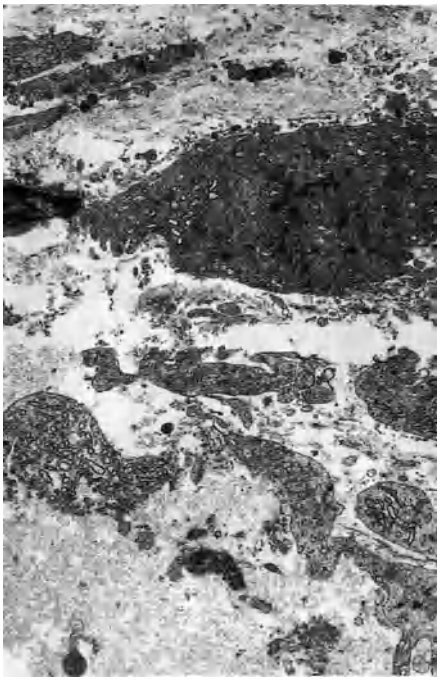

Fig. 6. Immature (undifferentiated) cells in granulation tissue of adriamycin-treated rats (7 days after implantation of spongiosa blocks). EM, x5 000

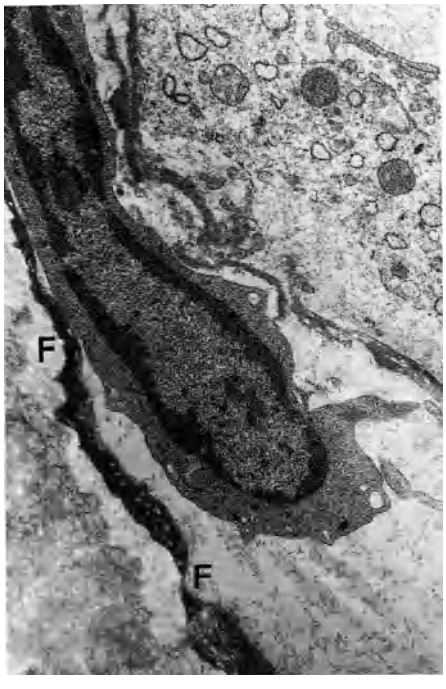

Fig. 7. Seven days after implantation – fibrin strands (*F*) of applied sealant are still visible in the adriamycin group

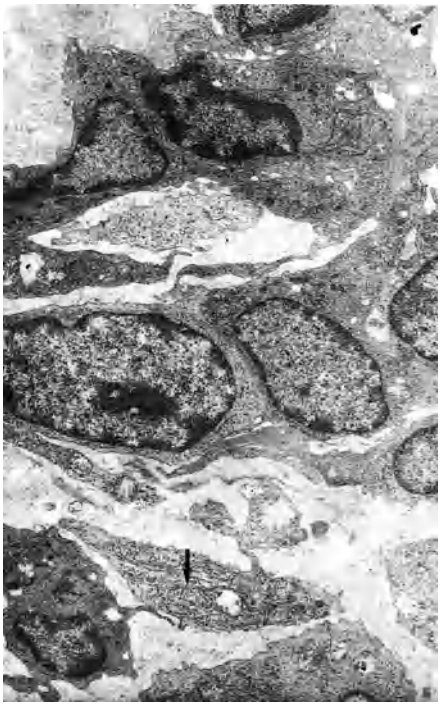

Fig. 8. Without adriamycin application fibrin is completely degraded after 7 days; mature cells are seen in which rough endoplasmic reticulum is already visible (*arrow*)

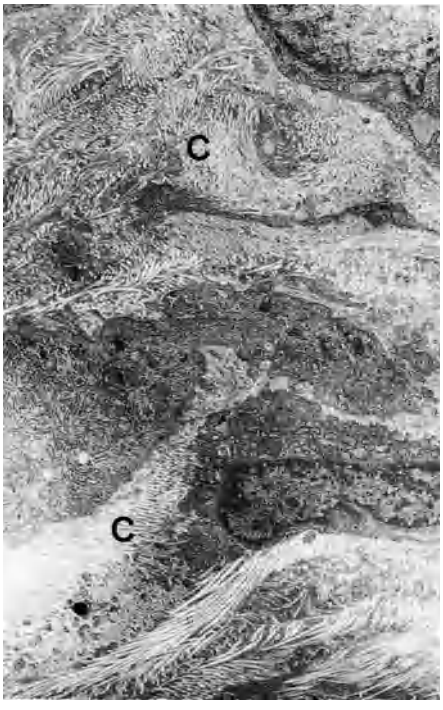

Fig. 9. Two weeks after implantation a marked collagen (*C*) structure is visible in the Tissucol group, which cannot be observed after adriamycin application

degraded (Fig. 8). After 2 weeks, a marked collagen structure was seen in the fibrin sealant group (Fig. 9); such a structure was not observed in the adriamycin-fibrin sealant group. In the latter group, many collagen-free zones were seen around the fibroblasts, as compared with a dense network of collagen fibers along the fibroblasts in the fibrin sealant group, which also showed abundant granular endoplasmic reticulum, corresponding to type B fibroblasts [1], as described in healing rat and human wounds [37].

It stands to reason that fibrin sealant cannot act on wound healing when cytotoxic drugs are applied simultaneously, since the fibroblasts are directly damaged. Nevertheless, in contrast to these findings, it has been shown that other forms of disturbed wound healing, such as ulcus cruris, can be cured by fibrin sealant in clinical settings, even when the ulcera have been unresponsive to other kinds of treatment [18].

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Fibrin Sealant and Its Modes of Application

H. REDL, and G. SCHLAG

Key words: antibiotics, collagen fleece, Duploject system, fibrin glue, hemostasis, spray, tissue adhesive, tissue sealing, wound healing

Abstract

After reconstitution, the two components of fibrin sealant – sealer protein/aprotinin and thrombin/$CaCl_2$ solution – can be applied in different ways. Besides sequential application or premixing of the reactant, application of the sealant components with the double-syringe applicator (Duploject) is advantageous in a number of ways, e.g., single-handed operation, thorough mixing, thin-layer application. Use of the Duploject is almost universally applicable. Thrombin concentration can be varied depending on the need for rapid or slow clotting of the sealants. The sealant can be delivered using needles, spray heads, or catheters, as indicated by the specific application. The spraying catheter can be easily used through the biopsy channel of an endoscope. Furthermore special micro-application techniques are possible. Fibrin sealant may also be used in connection with other biomaterials such as collagen (fleece), dura, and vascular grafts. Tests are reported on different collagen fleeces as well as on the addition of antibiotics. Finally visibility (including X-ray) and histological techniques are discussed.

The Material

Fibrin sealant is available under the trade names Tissucol, Tisseel, or Fibrin-kleber Human Immuno as a kit containing freeze-dried powder, freeze-dried thrombin, calcium chloride, and aprotinin solution. The substances mix to form two components: sealer and thrombin solution. To prepare the sealer, protein concentrate is dissolved in the accompanying stock solution of fibrinolysis inhibitor (aprotinin 3000 KIU/ml) or a dilution of it, where applicable. To simplify and speed up reconstitution (5–10) min of the highly concentrated sealer proteins, we developed a combined heating and stirring device – Fibrinotherm (Fig. 1). Thrombin is reconstituted in the accompanying 40 m*M* of calcium chloride solution, to yield concentrations of either 500 or 4 (NIH) units (NIH-U) of thrombin per milliliter depending on the chosen method of application. As the two components combine during application, fibrin sealant consolidates and adheres to the site of application, i.e., to the tissue.

The most important of the sealer proteins is fibrinogen, whose molecular weight is about 340 000 daltons. The molecule consists of six polypeptide chains of three different types – α, β, and γ. Through the action of thrombin, the fibrinopeptides A

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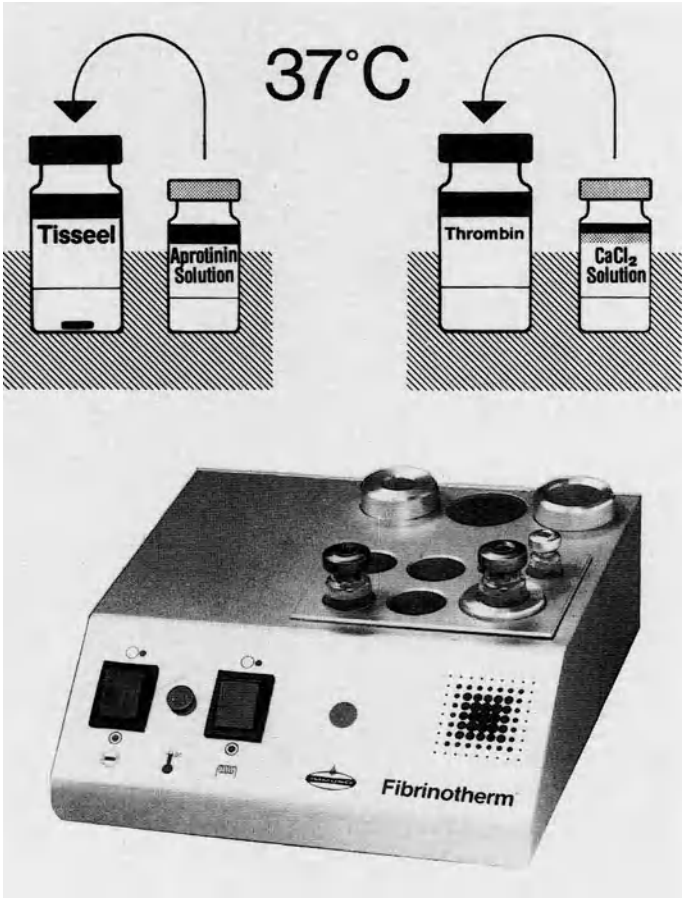


Fig. 1. Component preparation – Fibrinotherm

and B are split off from the resulting fibrin monomer. These fibrin monomers aggregate largely because of hydrogen bonding and thus produce the resulting fibrin clot. These reactions duplicate the last phase of the clotting cascade (Fig. 2). The time required for the onset of coagulation is dependent on the amount of thrombin used.

To achieve maximal tensile strength, cross-linking between fibrin α-chains is necessary. Fibrin seal itself contains sufficient factor XIII (which is activated by thrombin) to produce a high degree of cross-linking; the latter proceeds slowly, but the initial steepness of the α-cross-linkage curve results in sufficient tensile strength after about 3–5 min. In previous studies [1, 2], we were able to demonstrate the direct dependency of tensile strength on α-chain cross-linking. In other experiments [3, 4] we found that the intrinsic tensile strength of a clot formed with fibrin seal was about 1200 g/cm^2 (157 kPa) while that of a sealed rat skin was approximately 200 g/cm^2 (17 kPa) after 10 min cross-linking at 37°C, implying that adhesion of the sealant

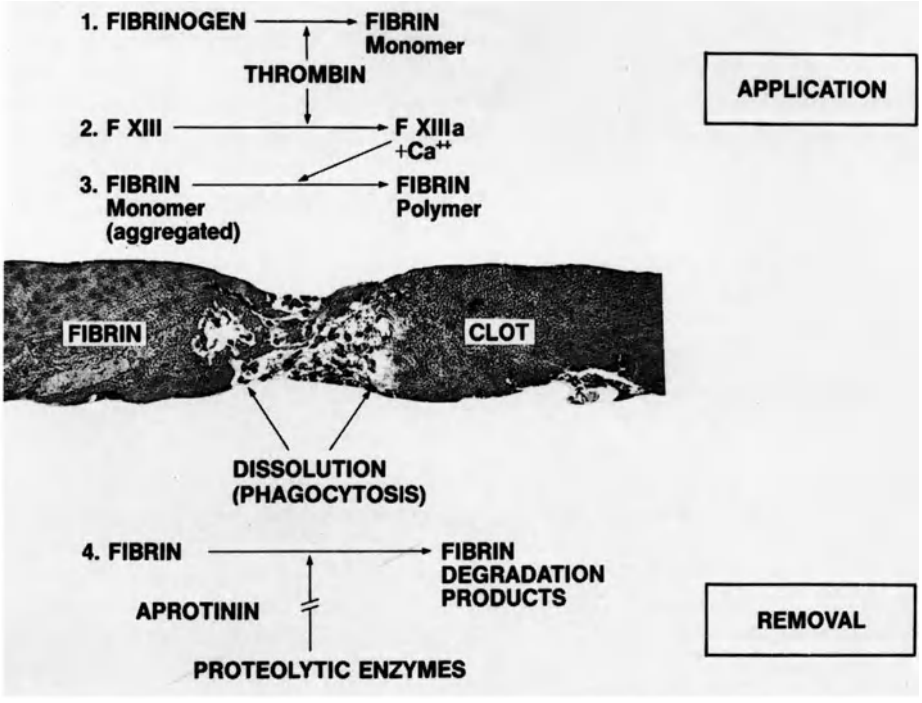


Fig. 2. Fibrin clot formation and removal

to the tissue is the decisive factor for gluing tissue. The adhesive qualities of consolidated fibrin sealant to the tissue might be explainable in terms of covalent bonding between fibrin and collagen [5] or fibrin, fibronectin, and collagen.

As far as the adhesive effect is concerned, critics have repeatedly pointed out its limited adhesive strength compared with synthetic acrylate adhesives. This is compensated for by the high elasticity of the material [6], which makes the material especially useful for nonstatic tissue, e.g., lung parenchyma. In addition, applications onto wet surfaces are equally possible, as is shown in Table 1. However, the applications of fibrin sealant are not limited to sealing severed tissue segments, as adequate hemostasis is also achieved.

Table 1. Tensile strength of sealed rabbit skin in relation to tissue moisture before application of Tisseel (method similar to that described by Redl et al.[26]

Dry (with pads)	Wet (with Ringer's solution)
× 48.2 g STD ± 10.7	53.3 g ± 12.8

To a variable extent, sealant persistence in vivo can be controlled by adding an antifibrinolytic agent [7]. Previous studies have demonstrated that aprotinin, a natural antiprotease, is superior to synthetic antifibrinolytic agents [8]; this has been confirmed by other reports [9]. Sealant degradation rate depends on

a) the fibrinolytic (or more generally the proteolytic) activity in the area of application,
b) the thickness of the sealant layer – which should be as thin as possible – and
c) the amount of aprotinin present.

Thus expected clot persistence can only be dealt with on an individualized basis. However, excessively long survival of the sealant may not be desirable [10].

Application of Fibrin Sealant

General

Historically the components were applied sequentially with relatively poor mixing owing to fast buildup of fibrin membranes between them. This prompted us to study mixing ratios, and alternative application techniques and their effects on the seal produced. Ever since the first applications of fibrin sealant the strength obtainable has been known to depend both on the fibrinogen concentration [11] and on the amount of cross-linkage [8]. Using a design for measuring intrinsic clot strength [3], we tried to find the optimum mixing ratio [12]. The mixture of one part sealant and one part thrombin solution gave the best results, although thorough mixing appears to be the decisive factor.

The gross and microscopic data obtained from experiments on rat skin revealed [12] that seals produced with premixed reactants (4 NIH-U thrombin/ml) or with the Duploject applicator (4 or 500 NIH-U/ml) had a superior tensile strength to those obtained with sequential application of reactants. There is no doubt that cavitation, as observed microscopically, is one factor involved. Another factor is insufficient availability of the reactants at the reaction site, since adequate cross-linkage requires a minimum concentration of Ca^{2+} [13], which may not be achieved locally if mixing is incomplete.

Duploject System with Needle

While we have repeatedly stressed the disadvantages associated with sequential application (poor mixing and cumbersome handling) [8, 12], the technique has not lost its role in selected cases, e.g., in combination with collagen fleece or vascular graft material so as to facilitate mixing.

In most cases, application of the sealant components with the double-syringe applicator (Duploject) is advantageous, e.g., single-handed operation, thorough mixing, and thin-layer applications. Use of the Duploject is almost universally applicable (Fig. 3).

Low thrombin concentrations (4 NIH-U/ml – slow clotting) are beneficial in all those applications where the parts to be sealed require subsequent adaptation, e.g.,

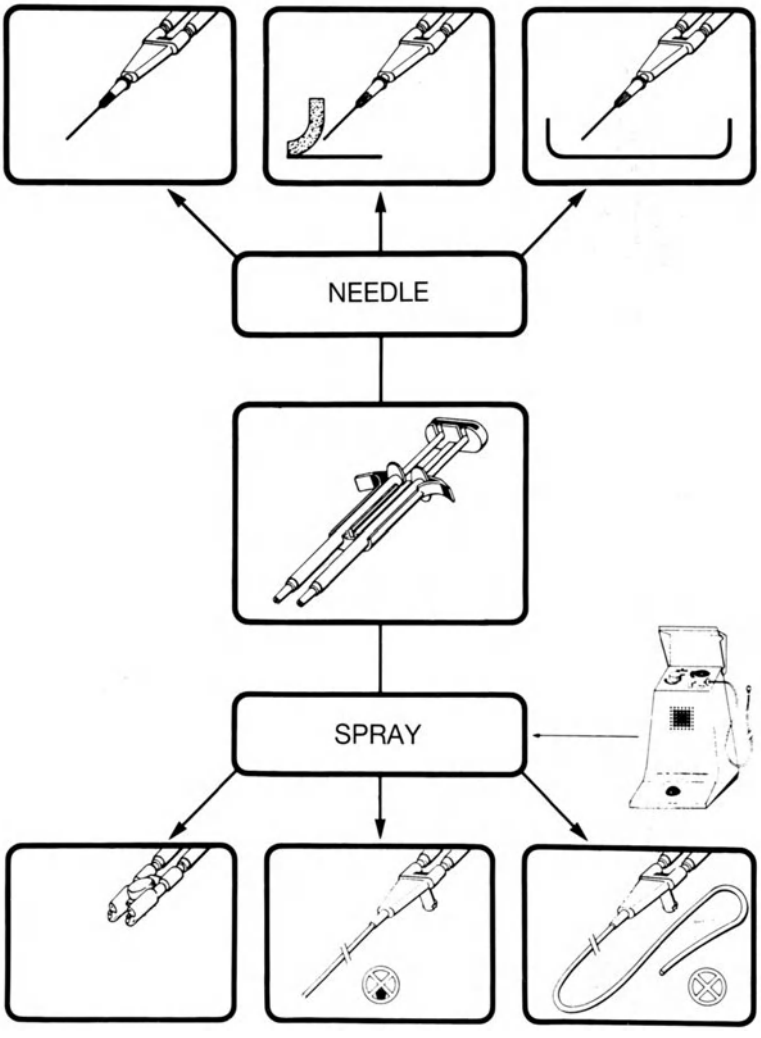
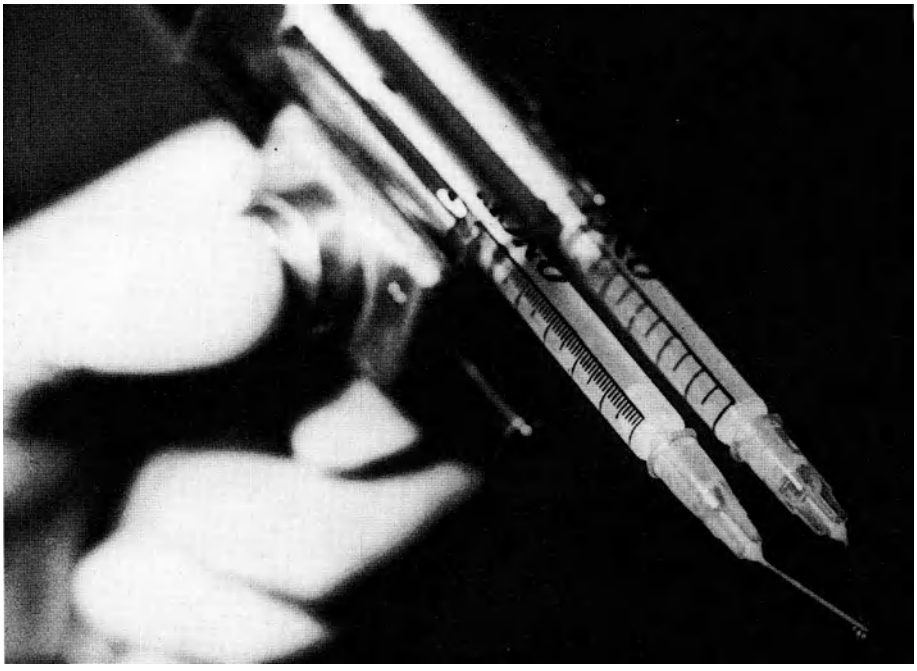


Fig. 3. Duploject system

in skin grafting and in some microsurgical operations. If, however, hemostasis is of primary interest, a high thrombin concentration, i.e., 500 NIH-U/ml, should be used as this ensures almost instantaneous clotting.

The double-syringe unit with mixing attachment – needle or catheter – is designed for simultaneous operation of the two barrels so that the two components are ejected at the same time but separately via the exchangeable mixing needle. As long as the sealant is being applied, there will be no clogging of the needle. Once application is interrupted, insertion of a new needle makes the applicator ready for use again.



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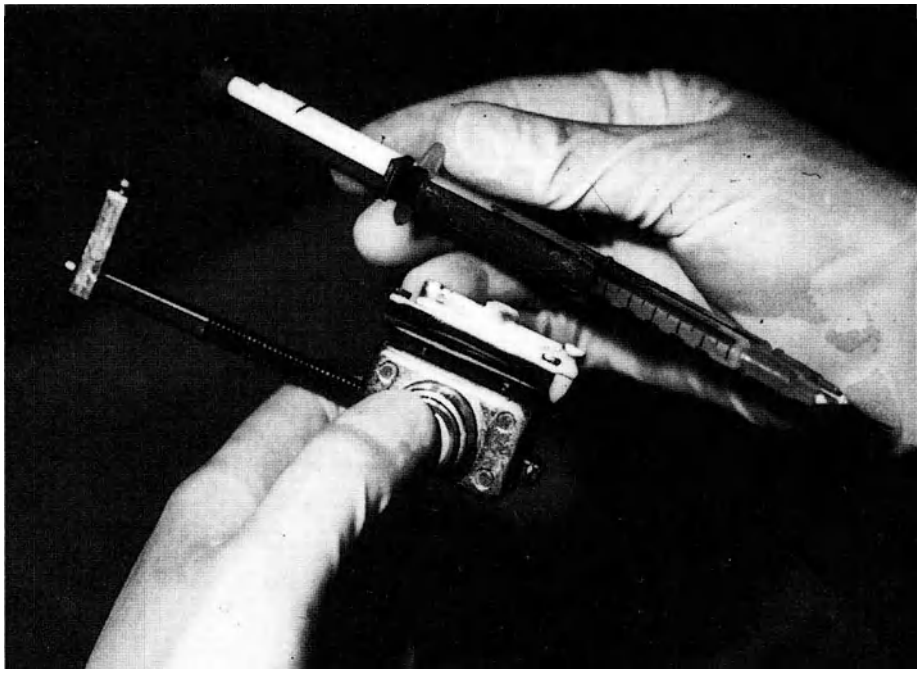

b

Fig. 4 a, b. Microapplicator to be used with Duploject system

Certain operations require the use of a microapplicator (Fig. 4) which allows repeated application of the same small volume per ejection; this is especially useful when using 4 NIH-U thrombin per milliliter. A similar system was developed by Tange [14]. An alternative is to mix the two components on a piece of aluminum foil and apply the premixed sealant with a spatula [15]. To get an "ultramicro" dosing (but without mixing) the special device of Chüden [16] may be used.

Duploject System – Spray Applications

The spray head or spray catheter (lower part of Fig. 3) is connected to a conventional pressurized gas source. The gas pressure is reduced to 2 bar (head) or 4 bar (catheter) in order to obtain a gas flow of 5–10 liters/min, which is optimum for use with the Tissomat (Fig. 3). The two components are injected separately into the continuous gas jet. The optimal distance between the spray head and the wound surface is approximately 10 cm for the head and 1 cm for the catheter. As the droplets bombard each other in the air and on the wound surface, they mix, and at a high thrombin concentration instantly form a delicate fibrin film. A thin film so produced is optimum and is required for the sealant to promote wound healing [10]. Spray head application also allows coating of extensive surfaces with a small amount of sealant. Thus an area of about 100 cm^2 can be coated with the 1-ml kit.

The spray head is especially useful for covering large areas, e.g., resected surfaces of parenchymal organs [17], for fixation of skin grafts and coating the donor area [18, 19], and for hemostasis of diffuse epicardial bleeding [20].

In the four-lumen spray catheter (Fig. 5), two lumens are used for the components, the third one for the gas, and in the short version a malleable wire is contained within the fourth lumen. The "spray catheter" can also be used, without spraying gas, to mix the two components in an otherwise inaccessible area, e.g., an esophageal-bronchopleural fistula [21]. In the latter case, the third lumen may be used to apply X-ray contrast dye for catheter localization.

Catheter spray systems can be modified to seal otherwise inaccessible areas by either:

1. The use of endoscopy (with biopsy channels) and a 150-cm-catheter (Figs. 5, 7), or
2. The short catheter with a malleable wire which allows any specific catheter shape (Fig. 6).

These catheters may be used for pleurodesis in recurrent pneumothorax [22–24], to occlude bronchopleural [25], rectovaginal, and esophageal-bronchopleural fistulas [26], to arrest gastric [27] and esophageal bleeding to ensure tissue sealing of the larynx, to fix flaps in plastic surgery, and to achieve hemostasis in epistaxis and after prostatectomy. An additional advantage offered by spraying with the Duploject spray is that the gas jet can be operated separately and can be used to clean and dry the operating site. The sealant is thus applied to a "dry" surface, which facilitates hemostasis. In addition, no clogging occurs when the sealing procedure is interrupted.

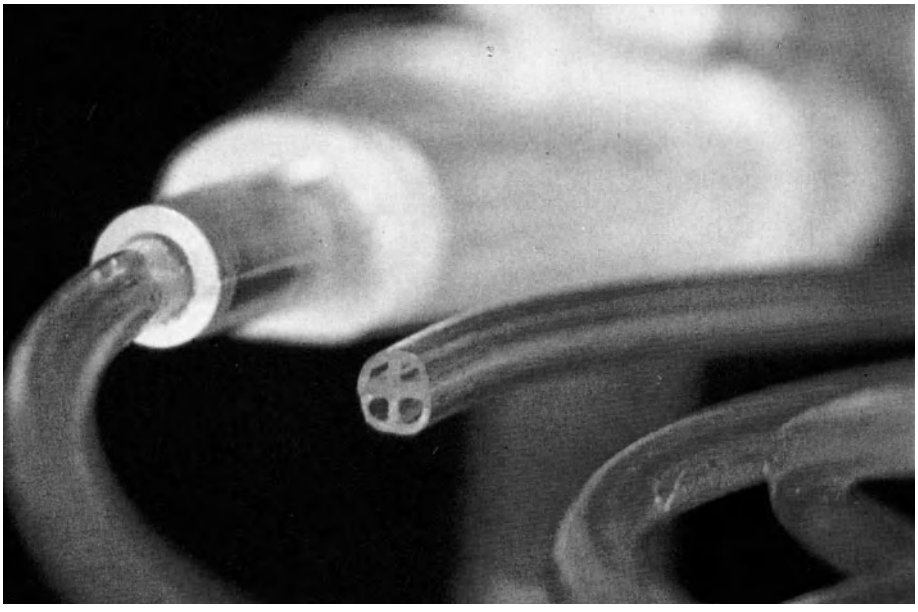

Fig. 5. Spray catheter with characteristic four-lumen design

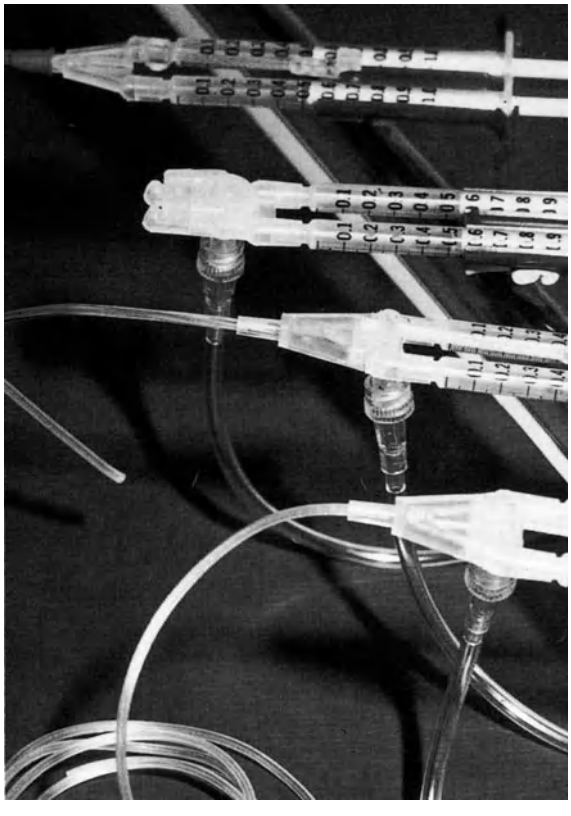

Fig. 6. Spray adaptors of the Duploject system

a

b

Fig. 7a u. b. Use of spray catheter through the biopsy channel of the endoscope. **a** Insertion into the channel. **b** Catheter in action, fibrin coming out of the biopsy channel at the tip of the bronchoscope

A cut Swan-Ganz catheter can also be used, as outlined by Linscheer [28]. This technique [15] has been successfully employed to treat patients with pneumothorax [29].

Combination of Fibrin Sealant with Matrices

For some applications the additional use of sealant support, e.g., Dacron patches, lyophilized dura, fascia, or collagen fleece, proved useful. However, not all of the commercially available fleeces are suitable for this purpose, and preliminary tests are therefore mandatory before clinical use. Some fleeces were tested by Stemberger [9] to assess their effects on platelet aggregation. We feel that pliable collagen fleeces are best suited for this purpose. Therefore we performed a preliminary study with some of the available fleeces. Test criteria were:

1. Uptake of liquid
2. Tensile strength in the wet state
3. Ease in handling
4. Tissue reactivity

Preliminary Results

1. To test the absorption of water, 1×1 cm pieces of collagen fleece of different thickness were used (for results, see Table 2). Absorption of H_2O was negligible with Collatamp and slow with Gelfix, all other fleeces absorbed H_2O immediately, which seems to be of essential importance in ensuring adequate soaking with sealant components. Some of the fleeces absorbed H_2O differently at the upper and the lower surfaces.
2. There were great differences in tensile strength in wet conditions (Table 2). Gelfix showed the highest tensile strength of all the fleeces tested. As expected, the Braun fleece had negligible tensile strength, whereas the Helitrex fleece of only 3 mm showed a remarkable tensile strength of 40–50 g.
3. Most of the collagen fleeces were easy to work with in wet conditions, with the exception of the Braun fleece, which broke into pieces and stuck to the gloves. (However, after our examinations had been completed, an improved fleece was developed.) The application of collagen fleece in dry conditions deserves special

Table 2. Test criteria and results of tests on different collagen fleeces in vitro

Company	Hydrophilic surface	Tensile strength	Handling	Tissue reaction
Braun	+	2 g	−	∅
Collatamp	−	10 g	+/−	+
Gelfix	−	150 g	−	+
Pentapharm	+	15 g	+/−	+/−
Helitrex	+	55 g	+	+/−
Savolon	+	50 g (inhomogeneous)	+	∅

mention, especially in regard to spray applications. The only fleeces suitable for this mode of application are Helitrex and Savolon 3 mm, whose properties with regard to ease of handling and H_2O absorption (in particular rapidity and volume of absorption of water) are excellent.

4. For histological examination, moistened pieces of fleece (size: 1×0.5 mm) were applied subcutaneously in rats according to a similar model of wound healing used by Rudas [30]. Blinding evaluation was performed after 14 days. The findings may be summarized as follows: In principle, every fleece tested was still detectable after 14 days; the larger pieces, however, were less disintegrated. The loosely textured Braun fleece and Savolon were absorbed relatively rapidly. The foreign body reaction seemed relatively limited with Braun, Savolon, Pentapharm and Helitrex, while Gelfix and Collatamp cause a more severe reaction. In view of our experience thus far, we recommend the use of Helitrex as a standard fleece for fibrin sealing. In addition to its properties outlined above, it has a further special property: if pressed in a dry condition it may be greatly compressed, yet when absorbing liquid, e.g., fibrin sealant, it expands to its original dimensions. This may result in interesting applications, e.g., endoscopy.

Combination of fibrin sealant with either decalcified bone (ongoing studies in this laboratory) or hydroxyapatite (see orthopedic section) is a further example of heterogenic combination. Fibrin sealant may also be used to fix bioprostheses, such as the middle ear bones [31].

Combination of Fibrin Seal with Antibiotics

The practice has been to apply fibrin seal only to areas unlikely to become infected. To overcome this limitation, the addition of antibiotics to the fibrin seal seemed desirable. As early as 1950 a patent was described in the USA in which the combined application of fibrin and antibiotics was used [32]. Fibrin seal has also been used in combination with antibiotics both experimentally and clinically [33, 34]. Therefore we studied the in vitro properties of mixtures of fibrin seal and antibiotics, particularly their effect on coagulation time, cross-linking, and drug release [3, 4].

For the practical application of fibrin seal, it is important to note that the clotting time can be regulated by the use of higher thrombin concentrations and the rate of fibrin-α-chain cross-linkage with additional factor XIII. Drug release from fibrin seal is probably by simple diffusion, and therefore to a large extent, dependent on the concentration gradient between the clot and its environment. This implies that although antibiotics incorporated into fibrin clots are retained for longer than when they are directly instilled into body cavities, drug retention is much lower than with bone cement-antibiotic mixtures and is insufficient to maintain adequate local drug concentrations for more than 3 days. This observation has also been confirmed in a recent in vivo study [35]. The limitations may be overcome by newer, less soluble antibiotics [36]. Nevertheless, infections may be controlled in the early stages after bone surgery using fibrin seal containing relatively high antibiotic concentrations. However, the total dose of drug should be less than the recommended maximal daily systemic dose.

Detection of Fibrin Seal in Tissues

Owing to the opaque white appearance of coagulated fibrin sealant, it is usually easy to detect fibrin in the sealing area. However, for special indications (e.g., in eye surgery) or with sequential application, in which one might wish to observe the delivery of the sealer protein solution, adding disulphine blue dye (ICI) (10 µl/ml sealer protein solution) is effective in rendering the fibrin seal visible.

For X-ray detection the addition of different contrast media was tested by Richling [37]. Metrizamide was found to be superior, but its general use cannot be recommended because of slight depression of fibrin-α-chain cross-linking.

Reviews on histological techniques for identifying fibrin sealant have been published by Dinges [30] and Heine [38]. With the phosphotungstic acid method of Mallory and the trichrome technique of Lendrum it is possible to visualize easily the fibrin sealant with light microscopy, but the fibrin sealant does not react as well as endogenous fibrin (perhaps due to the thicker network of fibrin strands). The histological differentiation between exogenous fibrin sealant and endogenous fibrin requires some experience if standard fibrin techniques are employed. If heterologous fibrin glue is used in animal experiments, its demonstration with the immunoperoxidase technique gives optimal results [30]. It is also easily seen with hematoxylin-eosin stain and shows up nicely on trichrome stain.

Conclusions

In summary, for the optimal use of fibrin sealant the application technique should meet the following requirements [12].

1. The sealant components should be fully dissolved and kept at a temperature of 37°C (which is easy with the Fibrino thermsystem — Fig. 7).
2. The wound surfaces should be as dry as possible (though application to wet surfaces is feasible).
3. The components should be thoroughly mixed on application.
4. The thrombin and aprotinin concentrations may be adjusted to the purpose of application.
5. The sealant should be applied as a thin film.
6. After clotting has occurred, further mechanical stresses should be avoided for about 3–5 min because of the time course of α-chain cross-linking.

Fibrin sealant is useful in controlling microvascular or capillary bleeding from ruptured or surgically dissected tissues. It is particularly beneficial in patients with increased bleeding tendencies undergoing surgery. It might also be used to seal tissue with different kinds of biomaterials. Thus fibrin sealant has a place in all surgical disciplines for the purposes of tissue sealing, hemostasis, and support of wound healing. There seem to be few drawbacks, not even such as the risk of viral transmittance [39, 40]; however, the benefits of combining fibrin sealing with modern-day surgery far outweigh any known risks.

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Properties of Different Tissue Sealants with Special Emphasis on Fibrinogen-Based Preparations

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Key words: fine clot, coarse clot, fibrin sealant, fibroblast proliferation, tissue adhesive, fibrinogen, wound healing, hemostasis

Abstract

Different tissue sealants are described with special emphasis on the performance of different fibrinogen-based sealants. Therefore the biochemical properties of four different fibrinogen-based tissue adhesives are compared in detail. The major difference is in clot structure – coarse versus fine. Related to this structural difference are additional dissimilar properties. The coarse type fibrin sealant proved to be superior in tensile strength, cell compatibility and fibroblastic proliferation.

Introduction

The use of tissue adhesives as an alternative method for repairing injured tissues, and more importantly, as a means for improving wound healing, may be based either on natural or synthetic materials. Therefore, it is necessary to compare various natural adhesives (e.g. fibrin sealant) to each other, as well as to synthetic preparations (e.g. cyanoacrylates), in order to asses their relative advantages and disadvantages in regards to clinical applicability (Table 1).

Table 1. Tissue Sealants

Synthetic	Natural
Acrylates	(Plasma)
Gelatine-Formaldehyde-Resorcin	(Cryoprecipitate)
	Fibrin Sealant

One obvious advantage of fibrinogen-based materials is their complete degradation and rapid removal from the body. Thus, local and systemic toxicity are avoided.

In the present study, we compare the biochemical properties of four different fibrinogen-based tissue adhesives; in addition, the similarities and differences of these natural adhesives, as compared to synthetic preparations, are discussed (Tables 2, 3).

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Table 2. Advantages and Disadvantages of Fibrin Sealant Versus Acrylates

	Fibrin sealant	Acrylates
Application to wet area	Possible	Impossible
Adhesivity	Good	Better
Elasticity	Very good	None
Tissue compatibility	Excellent	Poor
Absorption or degradation	Complete	None
Hemostasis	Excellent	None
Supporting of wound healing	Obtainable	Unobtainable
Application in bone and cartilage	Possible	Impossible
Foreign granulation tissue	None	Invariably present
Risk of virus infection	None*	None

*according to current knowledge

Table 3. Clottable Material [mg/ml]

Cryoprecipitate	AF	Fibrin sealant
29	11	80

Special emphasis is put on two fibrin sealants, which differ mainly in their ionic composition. Ferry and Morrison [1] described the influence of ionic strength on clot structure in 1947. High ionic strength results in "fine" clots and physiological ionic strength in "coarse" clots.

Material and Methods

The four fibrinogen-based, natural adhesives utilized in the study were cryoprecipitate, autologous fibrin (AF)[2] and two fibrin sealants. One fibrin sealant contains a physiological salt concentration (PS) while the second has a high salt concentration (HS) to achieve fast reconstitution.

Protein concentration and composition, kinetics of fibrin alpha-chain crosslinking, factor XIII content, conductivity and osmolarity were measured as described in Redl et al [3]. Intrinsic strength of the formed fibrin clots was tested in an apparatus similar to the one described by Redl et al]4], but using a 0.2 ml butterfly shaped mould for the breaking strength test and a larger one, 0.8 ml with 1.5 cm usable length, for elasticity measurements. The velocity used for stretching the fibrin clots was 1 cm/min.

Human diploid embryonal lung fibroblasts MRC5 were cultivated and their viability tested as described by Redl et al ([3]. Fibroblast proliferation was evaluated according to Mosmann [5] either on cell layers or in cell suspension using the substrate (3-(4,5 Dimethylthiazol-2-yl)-2,5-Diphenyl Tetrazolium Bromide) (Sigma, USA) (= MTT). The effect of the two fibrin sealants on fibroblasts was assessed in either a liquid or solidified state.

In order to assess the influence, if any, of the liquid sealants on the cells, the latter were seeded into the wells of TC Cluster 24 plates (Coster) and incubated at 37°C under 95% air + 5% CO_2 until an almost uniformly dense cell layer had formed. Following dilution of the sealants with equal volumes of isotonic NaCl solution, the cell cultures were covered with 0.5 ml of sealant solution for a maximum of 30 minutes. The effects of dilute sealants on the cells were observed using light microscopy and the supernatants removed at fixed intervals. The cells were then washed with isotonic NaCl solution and stained with Ziel-Neelsen Carbol Fuchsin (diluted 1:10 with water); micrographs were produced using a Polyvar microscope (Reichert).

The proliferation rate was determined according to Mosmann [5] and was used to obtain quantitative data. After incubation with liquid sealant as described above, 50 µl of MTT (5 mg/ml) was added and incubated further for 2^h at 37°C. Simultaneously 0.1 ml MRC5 cell suspension (5×10^5/ml) was added to 0.1 ml of each sealant solution, incubated for 30 min. and then incubated further at 37°C after the addition of 20µl MTT solution. The reaction was stopped with 0.4 N HCl in 2-propanol and the accumulated dye extracted. Photometric measurements were done after centrifugation of the supernatant fluid (diluted threefold with 0.4 N HCl/2-propanol) at 570 nm. This test has been shown to correlate well with the ^{3}H-thymidin uptake test [5].

In order to assess whether the solidified sealants differed in their influence on fibroblasts and to evaluate the fibrin structure, equal volumes of sealant solution were rapidly mixed at 37°C with thrombin-$CaCl_2$ solution (4 IU of thrombin/ml, 40 mmol of $CaCl_2$/l) and 0.5 ml of the mixture was poured into each TC Cluster 24 plate well (Costar) and incubated at 37°C and 100% rel. humidity for 1 hour. Plasma clots were produced similarly by mixing 0.9 ml of citrated human plasma with 0.1 ml of thrombin-$CaCl_2$ solution (4 IU thrombin/ml, 0.3 mol $CaCl_2$/l).

Some of the sealant clots were washed 4 times, each time with 0.2 ml of isotonic NaCl solution for 20 min at 37°C under continuous agitation; the washing efficiency was checked by washing clots of the same type with distilled water and determining the supernatant conductivity after each washing. The nonwashed clots and those washed with isotonic NaCl solution were each cut at a small angle (to obtain a rougher surface), covered with 0.2 ml MRC5 fibroblast suspension (5×10^5 cells/ml medium), and incubated for 24 hours at 37°C under 95% air + 5% CO_2. Direct examination of cells under the light microscope was possible only with the transparent HS fine clots, not with the milky white PS coarse clots. Therefore, the samples were prepared for histologic examination by fixing them in 3.5% formaldehyde solution followed by standard procedures of dehydration and paraffin embedding. For SEM examination, the samples were fixed with 1% glutaraldehyde (cacodylate buffer), refixed with 1% OsO_4, alcohol dehydrated, and critical point dried with CO_2. Dried samples were fractured in order to observe both surface and inner structures and gold sputtered (10 nm, Polaron Sputter) for scanning by a (Jeol-SM 35) SEM at 25 kV accelerating voltage.

Results

Cryoprecipitate and autologuos fibrin (AF) were found to have a low fibrinogen (clottable protein) concentration (Table 3), only moderate α-chain crosslinking (Table 4) and therefore only limited tensile strength (Table 5).

Both fibrin sealants require approximately the same reconstitution time (5–10 min) when PS dissolved at 37°C by using the combined warming and stirring unit described before [3] and HS at room temperature under manual shaking. Dissolution of HS at 37°C reduces the time required to 3–6 min.

PS and HS were found to be identical in their kinetics of fibrin crosslinking (Table 4) if FXIII is added to the latter.

Table 4. Crosslinking of Fibrin α-Chain (% of α-Polymer)

Incubation time (min)	Cryoprecipitate	AF	PS (coarse)	HS (fine)
120	35	36	80	80*

*(with additional factor XIII; see Table 6)

Intrinsic tensile strength was 4 to 5 times higher ($p < 0.001$, Student-t-test) in the PS coarse clots (Table 5). Due to the brittle nature of the HS fine clot, more than 50 % of the specimens broke during manipulation and were therefore excluded from the measurements. For the same reason, we were unable to obtain stress-strain results (length-tension relationships) of fine clots (Fig. 1). The decreased elasticity of the fine clots appeared to be unrelated to the fibrin sealant, as standard fibrin fine clots (with minimal lateral aggregation of protofibrils) were also irreversibly deformed, as compared to coarse type clots [6].

As was the case with fibrin structures, the different effects of solidified sealants on fibroblasts were best visualized on the cut surfaces of clots. On smooth PS clot

Table 5. Intrinsic Strength [g/cm^2] (kPa) (incubation temperature = 37°C)

Incubation time (min)	Cryo	AF	PS	HS
10	198 45* (19kPa) n=7	237 (23kPa) n=2	616+101 (60kPa) n=5	
30		not investigated	899+155* (88kPa) n=8	192+41** (19kPa) n=8

* = signif. p. < 0.001 Student t-Test
** = 50% of the fine clot samples had to be eliminated during machine set up

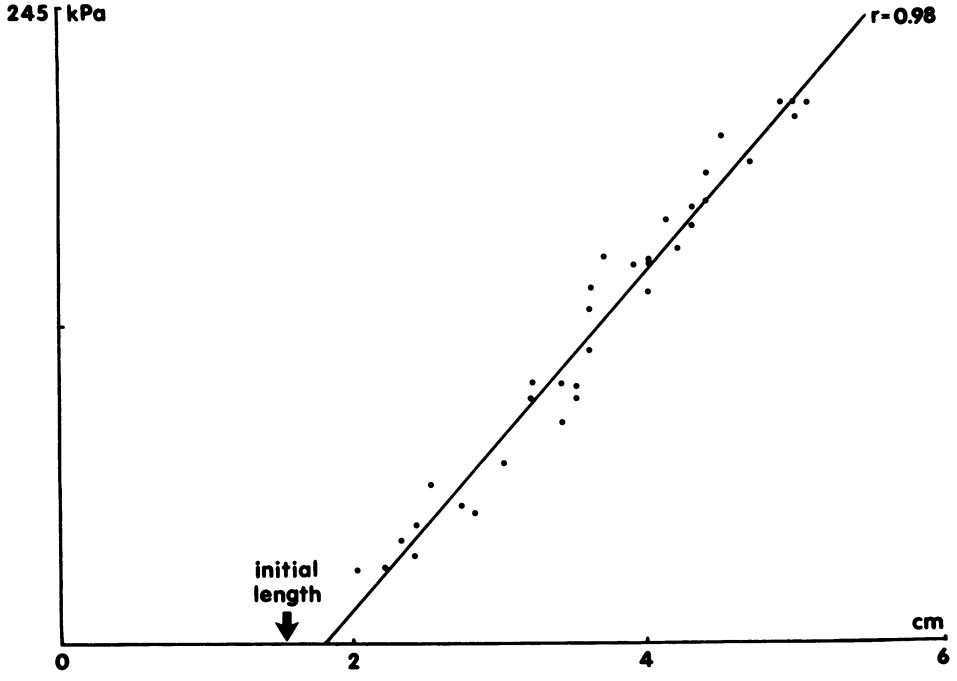

Fig. 1. Stress-strain diagram of PS coarse clot

surfaces, we observed a normal proliferation of fibroblasts. Mechanical disturbance of the clot surface greatly accelerated fibroblast proliferation, and the surface became completely covered with fibroblast growth (Fig. 2). HS clots treated in the same manner showed spheroidal deformation of cells, with no detectable proliferation (Fig. 3, Table 7).

The damage of cells on (nonwashed) HS clots was similar to the damage caused by the same sealant in liquid form, but the damaging effect occurred more slowly on the solid sealant.

Conductivity measurements on the supernatants of clot washings revealed the removal of more than 95% of salts contained in the clots after 4 washing cycles. Morphology and growth of fibroblasts were identical on washed and nonwashed PS clots, while the cytotoxicity of HS clots was reduced, but not completely eliminated, by extensive washing with isotonic NaCl solution (results not shown).

Table 6. Comparison of Fibrin Sealants

	PS	HS
Factor XIII (U/ml)	12.0	65.0
Conductivity (1:10 dilution with H_2O) (mS)	1.3	4.0
Osmolarity (mOsmol)	547.0	1 011.0

Fig. 2. Rich proliferation of fibroblasts on a cut PS clot. SEM, after critical point drying, x 1000

Fig. 3. Spheroidally deformed (damaged) fibroblasts on a HS fine clot after identical treatment as in Fig. 2

Table 7. Comparison of the Proliferation Rate of Fibroblasts (Cell Layer and Cell Suspension) when subjected to either PS or HS Sealer Protein Solution

	Photometric extinction at 570 nm		% Inhibition unphysiological – HS
	PS	HS	
Cell layer (mean of 3 diff. experiments ± SD)	.390±.130	.185±.077	53±3
cell suspension (mean of 3 diff. experiments ± SD)	.243±.190	.131±.112	67±7

Discussion

Because of the limited strength of Cryo and AF (Table 5), which results from a low clottable protein concentration (Table 3) and only ~ 35% α-chain crosslinking even after 2 hours (Table 4) no further experiments concerning histology and cell compatibility were carried out.

Fibrin sealant is a concentrated protein solution. Upon application, fibrinogen is coagulated by mixing with a thrombin-calcium chloride solution, following which the rigidity of the adhesives increases further as a result of fibrin crosslinking. The two preparations studied here produce clots with significantly different characteristics: PS clots are white (non-transparent) and of visco-elastic consistency, whereas HS clots are almost crystalclear and relatively brittle. Ferry and Morrisson [1] in 1947 described the formation of two different kinds of fibrin clots: white, non-transparent "coarse clots" formed at an ionic strength and pH value within the physiological range, and transparent "fine clots" produced at a higher ionic strength and/or pH value. Transition from one type to the other is smooth, with fibrinogen concentration, thrombin concentration, and reaction temperature as further influencing factors. In the present study, we determined electrical conductivity, osmolarity, and the kinetics of fibrin crosslinking of both sealants after adjustment of factor XIII content (Tables 4, 6). Micrographs of the fibrin clots produced were obtained under both light and scanning electron (SEM) microscopes and were compared with clots prepared from plasma and thrombin. Because HS differs from PS mainly by its high ionic strength outside the physiological range (causing the formation of almost amorphous clots), we examined the question of how the two sealants would differ in their influence on living cells. Considering the essential role of fibroblast proliferation in wound healing [7], we performed tests with human fibroblasts.

Our investigations were motivated by the striking differences in optical and mechanical properties between the two sealants after setting.

The essential difference between PS and HS is in ion content. PS conductivity is similar to that of isotonic saline solution, whereas HS conductivity is about three times greater.

Our results confirm the basic findings of Ferry and Morrison [1] that visco-elastic, nontransparent fibrin clots are formed at physiological ionic strength ("coarse" clots), whereas transparent, brittle "fine" clots are produced at a higher ionic

strength. Our results indicate that this influence of ionic strength persists over a wide range of fibrinogen concentrations.

Clots produced from PS or plasma show similar fibrin characteristics, consisting of relatively thick, branching strands (Fig. 4); HS clots appear almost amorphous under identical conditions (Fig. 5). The porosity of HS (with 4 IU/ml thrombin) seen in Fig. 5 might be even less when applied in vivo (with 400–500 IU/ml thrombin) as it was found by Blombäck et al. [8] that increasing thrombin concentration results in reduced porosity of fibrin clots.

Both sealants are very similar in terms of fibrin crosslinking kinetics. Ionic strength above the physiological range is known to inhibit fibrin crosslinking [9]; therefore this anticipated effect was compensated for by adding factor XIII.

The significantly higher tensile strength in the coarse clots (PS) is similar to previous shear modulus data from Kanykowski et al. [10]. The elastic rigidity measurements of fine clots (HS) revealed less than one-tenth the shear modulus found for coarse clots. It is possible that the rigidity of the latter clots is primarily due to steric immobilization as has been suggested by Nelb et al. [11].

Because mechanical union is just one aspect of successful surgery, wound healing and hemostatic properties of the sealants must also be simultaneously evaluated.

The formation of fibrin and its crosslinking by factor XIIIa are essential for wound healing. The fibrin network produced under physiological conditions serves as a

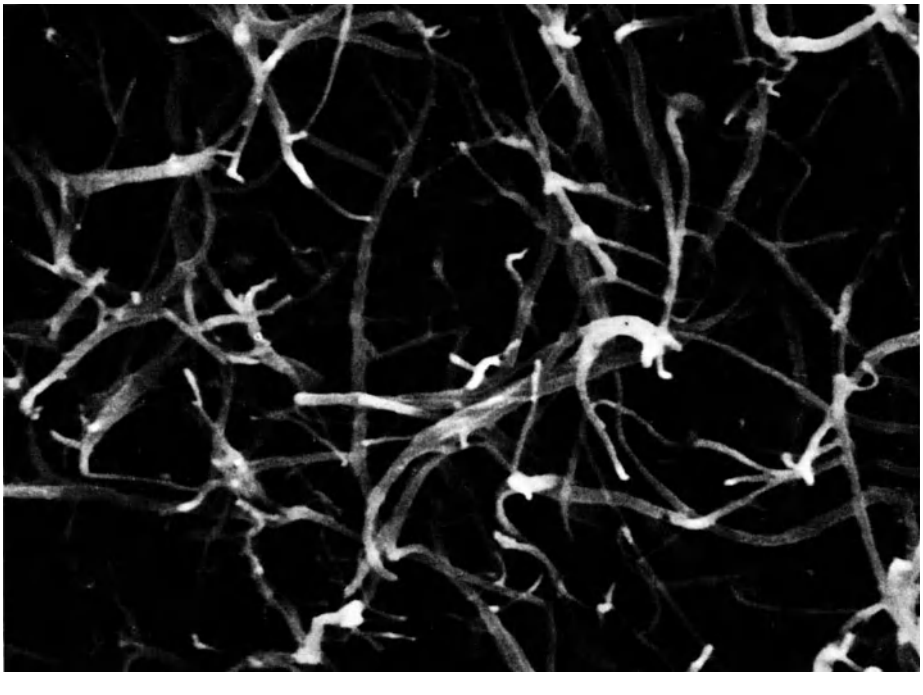

Fig. 4. Fibrin network in PS coarse clot very similar to plasma clot fibrin network. Scanning electron micrograph (SEM) after critical point drying.

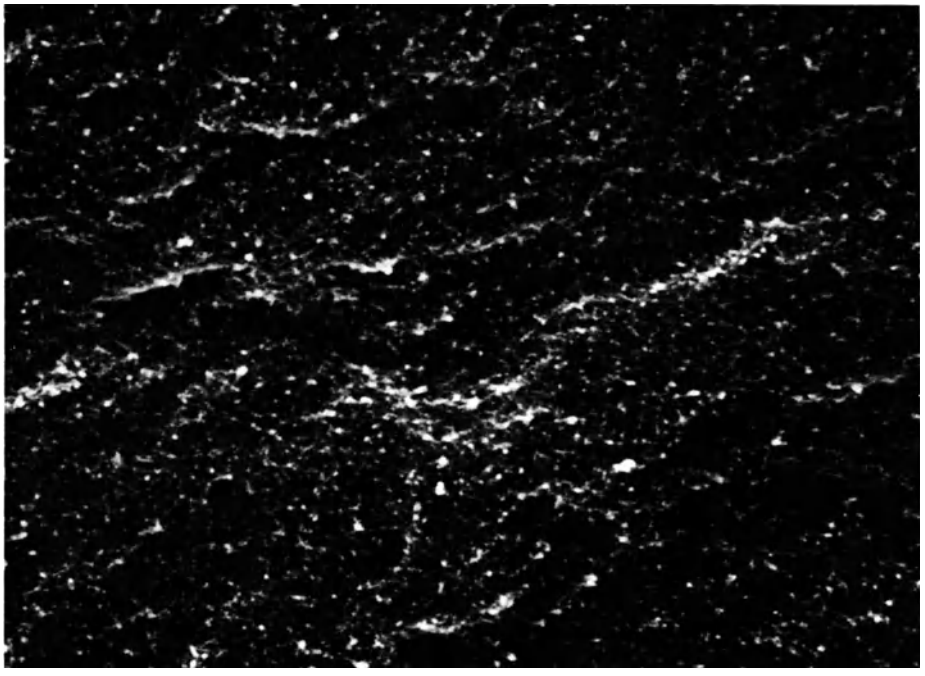

Fig. 5. Hardly detectable fibrin strands in a HS fine clot, conditions as in Fig. 4

matrix for the ingrowth of fibroblasts and the formation of collagen fibers [7, 12], thereby allowing for optimal wound healing. The formation of crosslinked fibrin is used not only for sealing tissues but for achieving hemostasis as well.

Up to now, many clinical and histologic reports [13, 14, 15, 16] describing satisfactory wound healing after fibrin sealant application have appeared. Thus the question arose whether the higher ion content of HS and the resulting altered fibrin structure of these clots influence fibroblast growth. Given the usual practice of mixing fibrin sealant with an equal volume of thrombin-$CaCl_2$ solution prior to application, we evaluated the influence of liquid sealants on fibroblasts after 1 + 1 dilution with isotonic NaCl solution. We found that human fibroblasts were severely damaged within minutes by contact with liquid HS, whereas liquid PS does not cause any detectable damage, even after prolonged incubation (Figs. 6, 7). The cytotoxic effect of liquid HS, which is also demonstrated by its 50–60% inhibition of cell proliferation (Table 7), is most easily explained by its high ionic strength and osmolarity. Both HS clots (nonwashed) and liquid HS cause similar damage to cells, but cytotoxicity develops more slowly with the clots. This is understandable if we assume cytotoxicity to arise from soluble additives; the solution trapped in the clot and the cell medium applied take a certain time to equilibrate, by when the damaging additives are further diluted.

In order to distinguish whether the cytotoxity of HS clots is due to soluble substances trapped in the clot or to the altered fibrin structure, we washed PS and

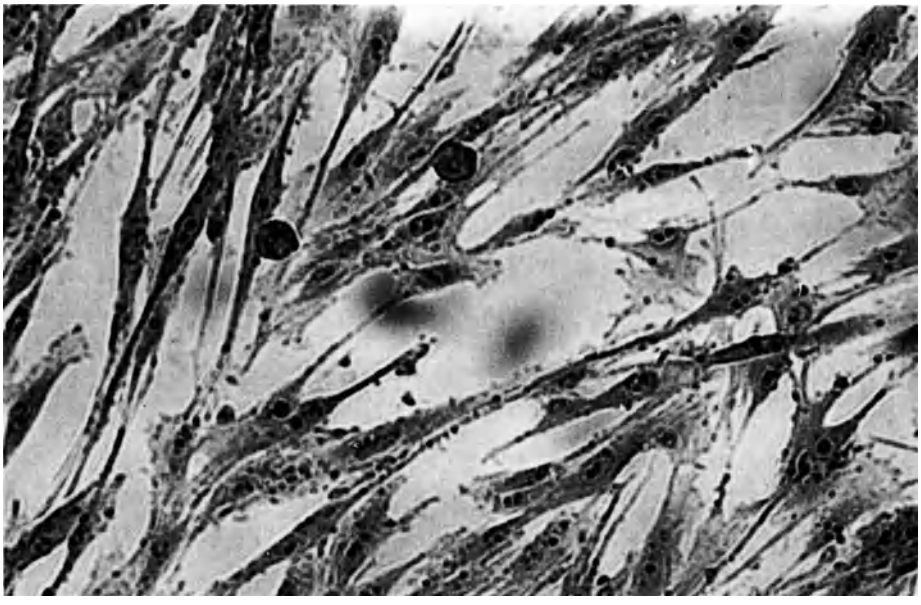

Fig. 6. Layer of fibroblasts 30 minutes after covering with PS, diluted 1 + 1. No detectable differences to controls. LM, carbol fuchsin staining, x 125

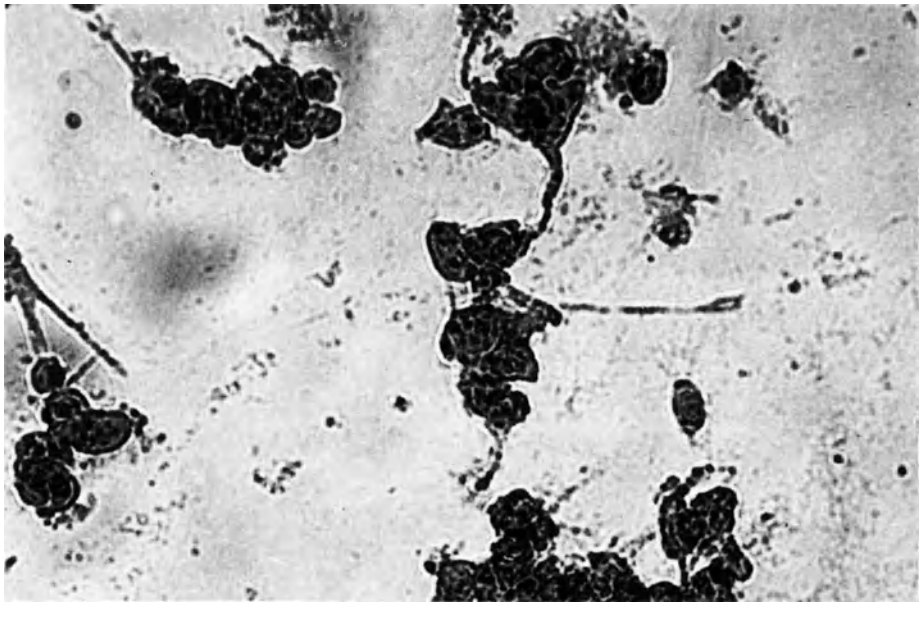

Fig. 7. Layer of fibroblasts 4 (!) minutes after covering with high salt concentration diluted 1 + 1. Damage to cell structure is clearly visible. Staining and enlargement as in Fig. 6

HS clots with isotonic NaCl solution. Conductivity measurements revealed that this procedure removed more than 95% of the conductive substances originally present in HS clots. Cells proliferated well on washed PS clots; washing reduced but did not eliminate cytotoxicity of HS clots [3].

Thus, the nearly absent structure of transparent fine clots appears to have a certain cytotoxic effect on fibroblasts in vitro. We consider this finding to have important implications in vivo. Although it may be assumed that the soluble components will diffuse out of a clot slowly, the typical "fine clot" structure will persist.

The importance of a stabilized fibrin network on fibroblast growth deserves special mention. The latter grow faster on cut PS clots than on the very smooth surfaces formed at the liquid-air interface of noncut clots. On the other hand, the same treatment on the cut surface did not improve fibroblast growth of washed HS concentration clots.

Beck et al. [17] in 1962 found that factor XIII is essential for normal fibroblast proliferation, they attributed the wound healing complications associated with factor XIII deficiency to a disturbance of fibroblast growth. These findings were later confirmed and extended by other investigators [18,19, 20]. According to Bruhn et al. [21], fibroblast proliferation is stimulated by the presence of factor XIII, whereas according to Kasai et al. [22], crosslinked fibrin rather than factor XIII is essential for the adherence of fibroblasts to the substrate and for well oriented cell growth. It was shown further that factor XIII itself may have an inhibitory effect on epidermal cell proliferation [23].

Our results indicate that crosslinked fibrin promotes attachment and growth of (human) fibroblasts only if present as PS coarse clots, whereas HS fine clots do not stimulate fibroblast proliferation and actually damage them, even at a comparable degree of crosslinking and after the additives that caused the formation of the fine clot structure have been removed.

Cryoprecipitate and glues from whole blood [2], carry other problems, such as poor standardization, lack of quality control, no virus inactivation, or little strength (e.g. AF, Table 5); the last point was corroborated by Hamm and Beer [24]. Other materials like COHN-fraction [24], though having good tensile strength, have very high viscosity as a major drawback.

It is obvious when comparing their different properties that synthetic sealants like acrylates [25] or gelatine-resorcin-formaldehyde [26, 27] have very limited applications.

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Lysis and Absorption of Fibrin Sealant (Tissucol/Tisseel)

(In Vitro and In Vivo Experiments)

H. PFLÜGER

Key words: Fibrin, wound repair, fibrinolysis, ^{125}I-elimination

Abstract

In order to determine the optimal fibrin thrombin adhesive system (FTAS) composition for resistance to fibrinolysis, in vivo lysis was tested by adding increasing amounts of the fibrinolysis inhibitor aprotinin to ^{125}I-FS; urokinase and plasminogen were administered in vitro while measuring protein and iodine^{125} release. The correlation between protein and iodine^{125} release clearly reflects the interdependence of these parameters; disjunction of radioactivity from the protein molecule was ruled out. In vivo, fibrinolysis is inhibited to a nearly unlimited extent by aprotinin. In vivo, aprotinin improves fibrinolysis inhibition only up to a maximum of 1500 KIU/ml clot, thereby significantly altering the maximum elimination of ^{125}iodine and FS half-life as well. Higher doses of aprotinin applied in vivo remain without effect upon FS stability. In human surgery, the addition of aprotinin to FS is recommended for strictly hemostatic application only, not for tissue synthesis such as nerve and microvessel anastomoses in plastic reconstructive surgery.

The aim of the second study was to investigate the degradation of fibrinogen thrombin adhesive system (FTAS) and the process of wound healing after partial kidney resection in rats using FTAS for induction of local hemostasis. In 28 rats partial kidney resection was performed bilaterally. Hemostasis was achieved with FTAS. Four experimental groups were formed. Group F (n = 3): hemostasis with unlabeled FTAS, subcutaneous injection of 0.1 ml = 60 μCi Na ^{125}I. Group G (n = 3): hemostasis with unlabeled FTAS, subcutaneous injection of 0.1 ml = 60 μCi ^{125}I-labeled FTAS, Group H (n = 6): hemostasis with ^{125}I-labeled FTAS. Group I (n = 16): treated like group H. In groups F–H ^{125}I elimination in 24-h urine samples was determined with a gamma-scintillation counter. Pairs of animals in group I were killed after 2, 6, 12, and 24 h and 3, 7, 14, and 21 days.

Kidneys were examined under the light and electron microscope and by autoradiography. In animals of groups G and H two peaks of ^{125}I excretion were observed: one peak within the first 48 h postoperatively which corresponded to the amount of free iodine injected with FTAS (FTAS contains 15% free iodine) and a second peak after 120 h which was most probably due to the degradation of FTAS. Fibrinolysis was not observed. FTAS was resorbed mainly by macrophages. The time course of wound healing paralleled that of physiological fibrinogen concentration. Renal parenchymal damage was not observed.

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Introduction

Fibrin plays a central role in the physiological process of wound healing. According to examinations by Key [8] fibrin induces the chemotaxis of polymorphonuclear granulocytes and introduces the initial inflammatory phase of the healing process. There is no doubt that the concentration of fibrin and the platelet content of the thrombus as well as a variety of other factors are in direct interaction and influence the duration of the healing process.

Use of Tissucol, a sealing method that has been employed for years, imitates the physiological process, applying unphysiologically high concentrations of fibrinogen. The influence of the artificial clot on chemotaxis and the resulting induction of macrophages and fibroblasts and of collagen fiber formation is unknown. Other unanswered questions are

a) the importance of the local potential of the sealed tissue for lysis and degradation of the fibrin clot and
b) the necessity of adding fibrinolysis inhibitors to the film clots and their appropiate concentrations. It was the objective of the experiments described below to test the fibrinolysis of a Tissucol clot in vitro with and without proteinase inhibitors, and to obtain further results on cellular fibrin degradation in in vivo experiments.

First Study

Materials and Methods

In Vitro Experiment

0.1 ml ^{125}I-FS Human Immuno (60 µCi/0.1 ml) was clotted by adding 0.1 ml thrombin (4 NIH-U/ml) and $CaCl_2$ (0.04 *M*/Liter) and incubated for 30 min at 37°C. Aprotinin (5000 KIU/ml clot) was added to series A. There was no aprotinin in series B.

In vitro lysis of FTAS was performed by layers of 1 ml urokinase (5.25 Plough-U/ml) and 1 ml plasminogen solution (0.2 CTU/ml) at 37°C permanent incubation. The supernatant was exchanged every 12 h. Protein content was established photometrically at an extinction of 280 nm, and the content of ^{125}I was measured by a gamma-scintillation counter.

In Vivo Experiment

Twenty-one albino rats (Wistar) with an average weight of 320 g were used as test animals. The animals were kept in single metabolite cages and fed with Tagger whole food and water ad libitum. In order to avoid any intermediary retention of ^{125}I in the thyroid gland, the animals were given 25 drops of Lugol's solution (ÖAB 9, solutio jodi aquosi) in 40 ml drinking water 3 days before the tests were started. In Ketalar (60 mg/kg body weight) and Rompun (8 mg/kg body weight) general anesthesia, two skin pockets of 1.5×0.5 were formed on the back of the animals and 0.2 ml FTAS was injected into these pockets.

Fibrin sealant:
0.1 ml ^{125}I-FS human Immuno (60 μCi/0.1 ml)
0.1 ml thrombin (4 NIH-U/ml)
$CaCl_2$ 0.04 *M*/liter

Group C ($n = 7$) was treated without aprotinin, while in group D ($n = 7$) 1500 KIU/ml clot and in group E $n = 7$) 5000 KIU/ml clot were added to the FTAS. In animals of group C–E ^{125}I elimination was counted by gamma-scintillation counter in urine collected over 24 h until the 7th day after surgery.

All the results were indicated as mean value with standard deviation.

Results

In Vitro Experiment

The correlation coefficient of protein concentration (extinction at 280 nm) and radioactivity counted was $r = 0.97$ for both series A and series B. Regression line $y = 0.02 \times + 0.04$ (Fig. 1).

The samples with aprotinin (series A) showed slow fibrinolysis. A maximum of 5% of the total activity was absorbed per 12 h and the stability of the clot lasted for more than a week. In the samples without aprotinin (series B) the maximum degradation was found after 36 h, 40% of the total activity being released (Fig. 2). After 60 h the whole FS clot was dissolved. All the animals survived the surgical intervention and the observation period of 7 days.

The maximum ^{125}I excretion in animals of group C was found after 1.75 ± 0.5 days, in group D (1500 KIU/ml clot) after 3.2 ± 0.45 days, and in group E after 3.5 ± 1.29 days.

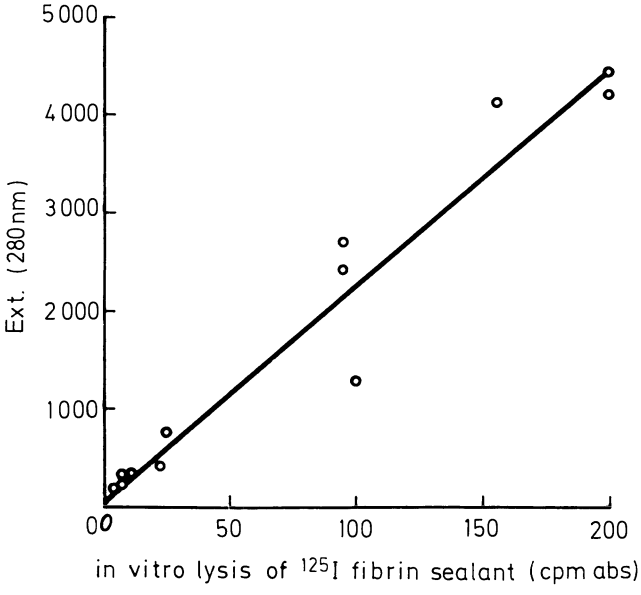

Fig. 1. Correlation of protein concentration and counted radioactivity. Measurement every 12 hours after lysis of a ^{125}I. Fibrin sealant clot with urokinase – plasminogen

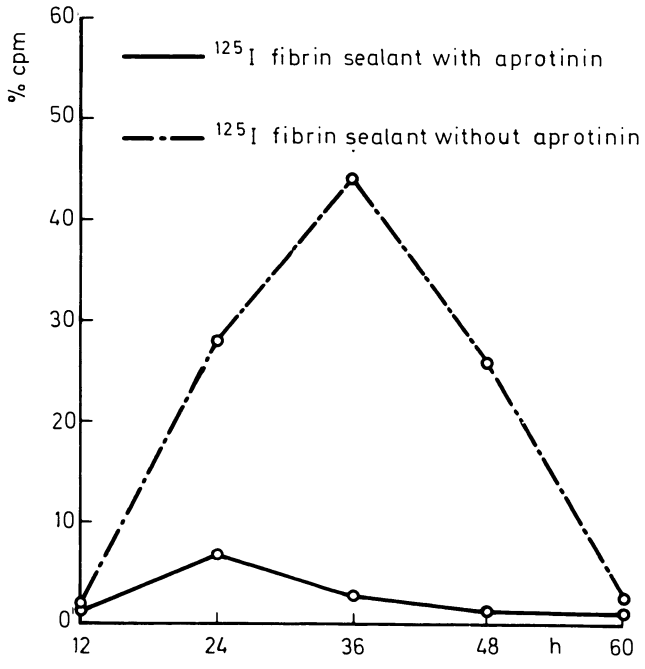

Fig. 2. Fibrinolysis expressed in radioactivity counted in 24h urin samples of rats

Statistical evaluation of the results by means of the hour *t*-test showed a significant time difference in the elimination maximum ($p<0.01$) between animals of groups C and D, and C and E. Comparison of the groups D (1500 KIU/ml) and E (5000 KIU/ml) showed no significant time difference in the ^{125}I excretion maximum. (Fig. 3) shows mean values of ^{125}I elimination as a percentage of the total dose applied in animals of groups C and D during an observation period of 7 days. In animals of

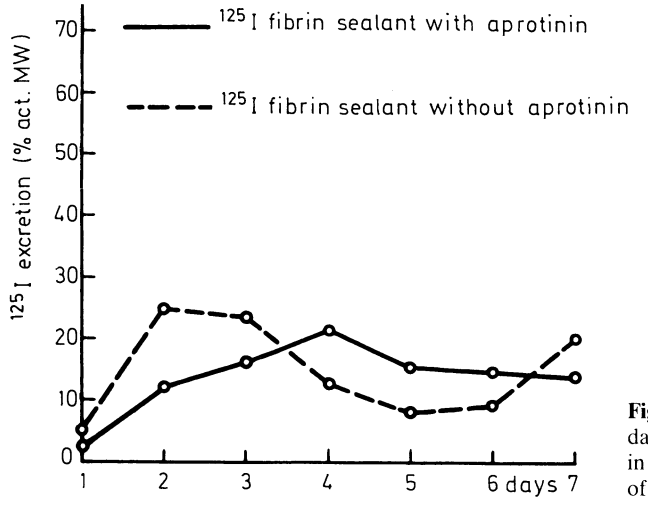

Fig. 3. Mean values and standard deviation of ^{125}I.-excretion in 24h total urin, indicated in % of total excretion per 10 days

group C we found a two-stage course of the graph: A first elimination peak occurred after 2 days ($\bar{x}$~24%); ^{125}I excretion then reached a minimum on the 5th day after surgery ($\bar{x}$~8%) but a further increase was observed on the 7th day after surgery ($\bar{x}$~20%). In animals of group D this two-stage course of the graph could not be observed. They showed a slow increase in ^{125}I excretion, the peak being on the 4th day after surgery ($\bar{x}$~21%), as well as a slow decrease in ^{125}I excretion. On the 7th day after surgery 14% of the total dose applied was eliminated. ^{125}I elimination in animals of group E was almost identical to that in animals of group D.

FS Half-life

The Half-life (period of time after which half of the iodine dose applied has been eliminated) was 2.16 ± 0.13 days in animals of group C, 2.82 ± 0.31 days in group D, and 2.92 ± 0.25 days in group E. There was a statistically significant difference ($P < 0.01$) between animals of groups C and D, and groups C and E. There was no statistically important difference between groups D and E.

Second Study

Materials and Methods

In the second study we examined the degradation of fibrinogen thrombin adhesive system (FTAS) during healing after partial kidney resection in rats, using FTAS for production of local hemostasis. We followed the fate of the autologous fibrin clot histologically and by monitoring the redistribution of ^{125} iodinated fibrin fragments.

FTAS was applied on a supporting collagen fleece (Disperger, Vienna), placed on the resection wound [12], and lightly pressed digitally on to the resection area for 60 s. Twenty-eight male albino rats were used (Wistar SPF breed, average weight 350 g). The animals were kept in single cages and fed with Tagger complete food and water ad libitum. In order to achieve complete blockage of iodine absorption into the thyroid gland, all animals were given 25 drops of Lugol's solution (ÖAB 9, solutio jodi aquosi) in 40 ml drinking water 5 days before starting the experiment. Under diethyl ether anesthesia the kidneys were exposed through lumbar incisions, bilateral lower partial kidney resections were performed, and hemostasis of the parenchymatous wound was achieved with FTAS as described above. Twenty percent of the renal parenchyma was removed. The 28 animals were divided into four experimental groups:

Group F (n = 3): Bilateral partial kidney resection, hemostasis with unlabeled FTAS, subcutaneous injection of 0.1 ml = 60 μCi Na ^{125}I (Amersham, IMS, 1 P ^{125}I sodium thiosulfate).

Group G (n = 3): Bilateral partial resection, hemostasis with unlabeled FTAS, subcutaneous injection of 0.1 ml = 60 μCi ^{125}I-FTAS.

Group H (n = 6): Bilateral partial kidney resection, hemostasis with ^{125}I-FTAS.

Group I (n = 16): Bilateral partial kidney resection, hemostasis with ^{125}I-FTAS.

The ^{125}I-elimination in a 24-h urine sample from animals in groups F–H was measured by a gamma-scintillation counter daily up to the 10th postoperative day.

For morphological studies pairs of animals of group I underwent laparotomy 2, 6, 12, and 24 h and 3, 7, 14, and 21 days after surgery. The kidneys which had been partially resected were perfused with Hanks' solution to remove all intrarenal blood and then perfused for 10 min with 2.5% glutaraldehyde in 0.1 *M* cacodylate buffer (pH 7.4) [9]. The tissue samples were embedded in Epon 812 and 1-μ m sections were stained with 1% toluidine blue. For autoradiography Kodak Nuclear Track-Emulsion was applied to the sections, the exposure time being 28 days at 4°C. Ultrathin sections were examined in an EM9S electron microscope.

Serum creatinine and BUN were determined photometrically on the 3rd and 10th postoperative days.

Results

General

No animal died immediately after operation or within the period of observation. Three animals developed a unilateral wedge-shaped, ischemic renal infarction. Parenchymatous destruction to a maximum depth of 3–20 tubular lumina could be found in all other kidneys. In two cases a stone was found in the renal pelvis. Diffractometric X-ray analysis showed the stone composition to be calcium oxalate monohydrate. No animal developed uremia.

Dynamics of ^{125}Iodinated FTAS and ^{125}I Sodium Thiosulfate

Mean values and standard deviations of the ^{125}I excretion in 24-h urine samples indicated as a percentage of the ^{125}I total excretion during the 10-day observation period for animals of groups F–H are shown in Fig. 4.

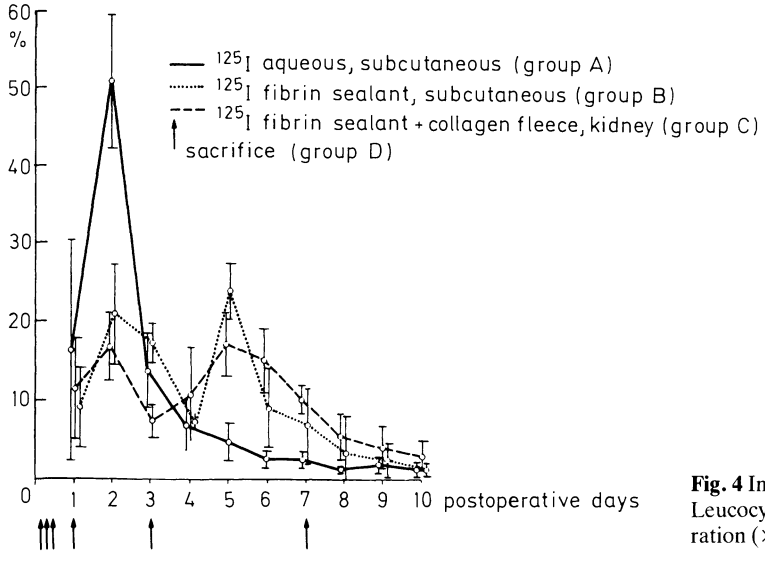

Fig. 4 Imigration of Leucocytes 24^{h} after operation (× 4.500)

Group F (Subcutaneous Injection of 60 μCi Na ^{125}I)

^{125}I excretion was maximal on the 2nd postoperative day (50.5 ± 8.4%) and an exponential decrease of ^{125}I elimination occurred after this time. By the 3rd postoperative day 80% of the measured total dose had been eliminated. ^{125}I elimination on the 10th postoperative day was 1.5 ± 0.75%.

Group G [Subcutaneous Injection of 0.1 ml (Containing Approximately 75 mg Protein) = 60 μCi FTAS]

Maximal ^{125}I excretion occurred on the 2nd (20.6 ± 6.2%) and 5th postoperative days (23.6% ± 3.5%). The least ^{125}I elimination occurred during the 4th postoperative day (7% ± 1.3%). A slow decrease in ^{125}I elimination occurred from the 5th postoperative day onwards. ^{125}I excretion on the 10th postoperative day was 1.1% ± 0.6% of the measured total dose.

Group H ^{125}I-FTAS for Hemostasis of Kidney Wounds

Maximal ^{125}I elimination occurred on the 2nd (16.5% ± 4.2%) and 5th postoperative days (16.5% ± 3.8%). The lowest excretion rate occurred on the 3rd postoperative day (7.3% ± 2%). A slow decrease in ^{125}I elimination occurred after the 5th postoperative day. ^{125}I elimination on the 10th postoperative day was 3% ± 2% of the measured total dose excreted.

Radioisotope excretion did not depend on the daily volume of urine.

Histological, Electron Microscopic, and Autoradiographic Findings in Animals of Group I

2, 6, and 12 Hours After Operation. No reaction of connective tissue was observed under the light or on the electron microscope. Collagen fleece was inhibited with erythrocytes and partly lifted off the parenchymatous area by small hematomas.

24 Hours After Operation. Light and electron microscope studies showed emigration of neutrophilic granulocytes and macrophages into the intersticium (Fig. 5). Autoradiography showed larger amounts of labeled fibrin at the area of adhesion.

3 Days After Operation. Cell-rich granulation tissue and infiltration of granulocytes was seen under the light microscope (Fig. 6). Marked resorption of fibrin clots by phagocytosing macrophages (Figs. 7, 8), as well as capillary outgrowth, was seen under the electron microscope. A high concentration of radioactively labeled FTAS was still present.

7 Days After Operation. Collagen fiber appeared and isolated remnants of radioactively labeled fibrin were seen in the granulation tissue with numerous macrophages.

14 and 21 Days After Operation. Collagen-rich granulation tissue with a markedly decreased number of infiltrating cells was found. Until the 14th postoperative day,

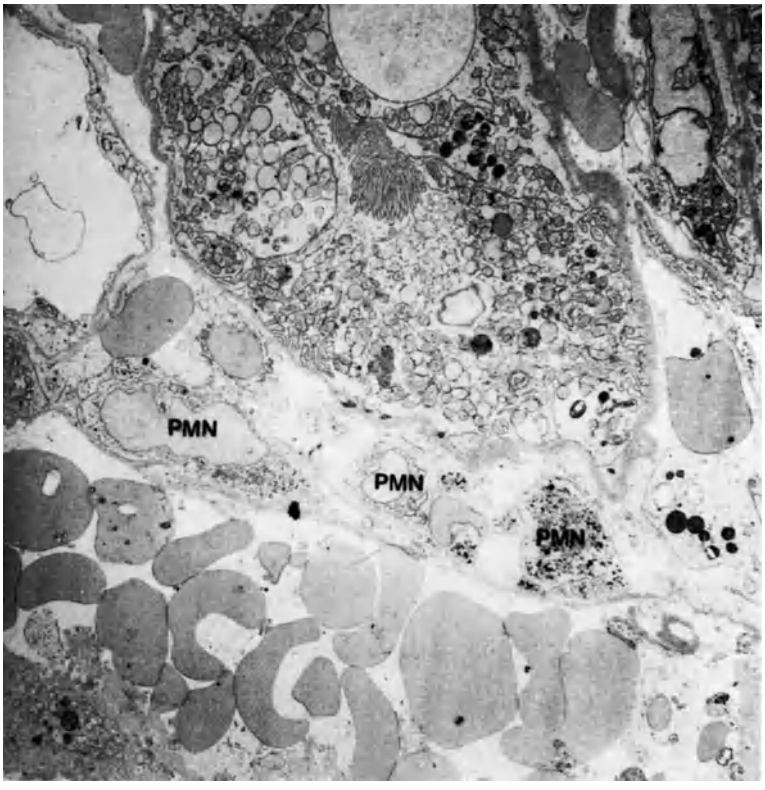

Fig. 5. Cell rich granulation tissue and Leucocytes 3 days after Operation (× 32)

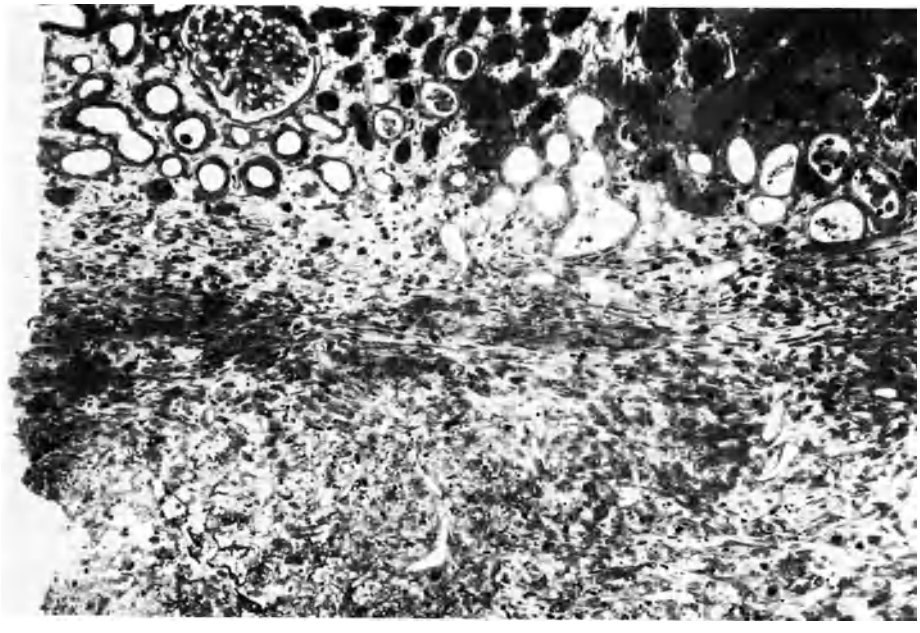

Fig. 6. FTAS-resorption by macrophages 3rd postoperative days (c 5.700)

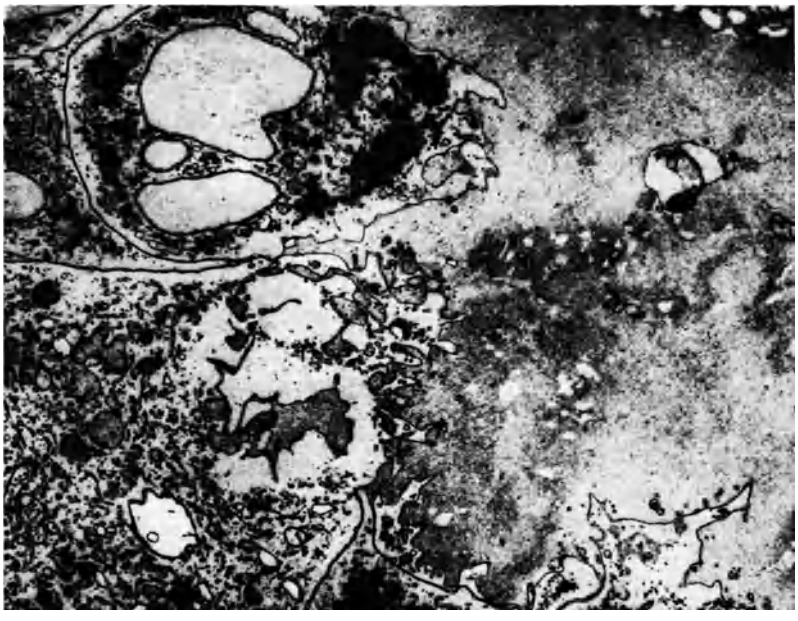

Fig. 7. Partial enlargement of Fig 6 (× 27.000)

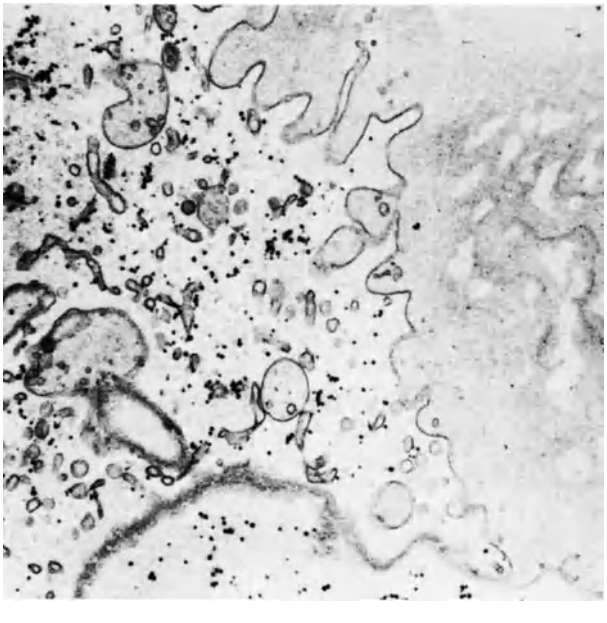

Fig. 8. Macrophages with stored labeled FTAS-degradation products 14^{rh} post-operative day (×320)

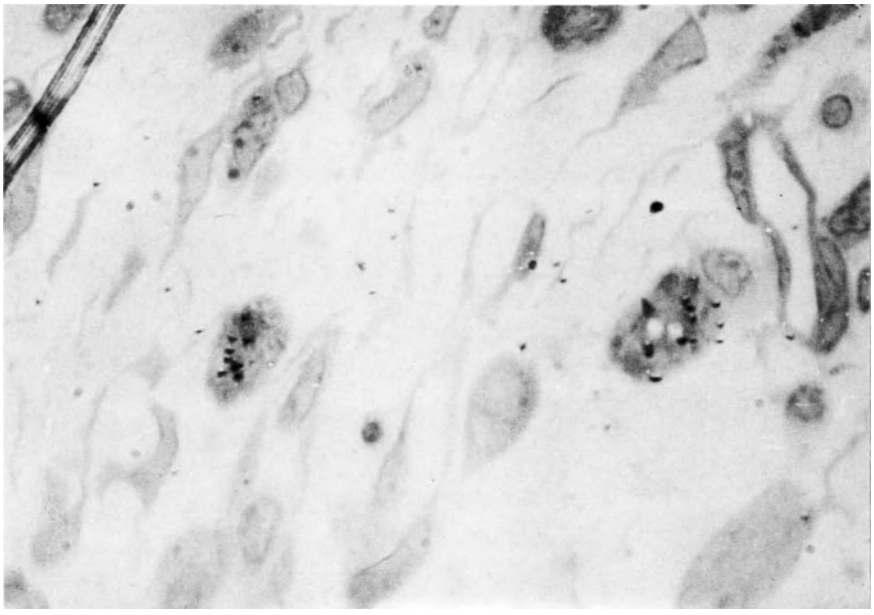

Fig. 9. Macrophages with incorporated degradation products of ^{125}I-labeled fibrin sealant

radioactively labeled fibrin was found in macrophages (Fig. 9). There was decreasing infiltration of round cells.

Discussion

Urokinase plasminogen-induced in vitro lysis of ^{125}I-labeled fibrin sealant shows an excellent correlation of both measuring parameters after measuring protein content and released radioactivity. This seems to prove that in vitro ^{125}I is not balanced out and washed off by protein molecules. It has to be presumed that measurements of ^{125}I excretion in 24-h urine in vivo are directly proportional to clot degradation.

In vitro the resistance of FS to urokinase plasminogen-induced lysis may be increased most efficiently and for as long as is wanted by the addition of aprotinin [6,11]. Measurement of ^{125}I activity released in series A and B supports these findings. As expected, the in vivo experiment showed that FTAS with aprotinin (1500 KIU/ml clot) is more resistant to fibrinolysis than FTAS without aprotinin. Increasing the aprotinin concentration to 5000 KIU/ml clot does not cause a delay in the ^{125}I elimination maximum nor any prolongation of the biological half-life. This seems to prove that aprotinin (1500 KIU/ml clot) is sufficient for stopping local fibrinolytic activity, and that the physiological degradation of FTAS by phagocytosis cannot be influenced by aprotinin.

^{125}I is mostly excreted in the urine after absorption of labeled iodine into the thyroid gland has been prevented by prior oral administration of an overdose of stable iodine. Analogous to the in vivo examinations by Alkjaersig [1] and Dudock

[4, 5] the determination of ^{125}I elimination in urine provides information about the degradation of labeled fibrin clots.

After subcutaneous injection, ^{125}I sodium thiosulfate was eliminated in the urine maximally on the 2nd postoperative day (50.5% ± 8.4% of total elimination per 10 days) in a single peak, reflecting the elimination pattern of free ^{125}I sodium thiosulfate. By contrast, after subcutaneous injection of ^{125}I-FTAS (Group G) and also after application of ^{125}I-FTAS in a collagen fleece directly to the renal parenchyma (group H) there were two peaks of ^{125}I excretion, one on the 2nd and one on the 5th postoperative day. The first peak after 2 days corresponded with the maximal excretion of unbound iodine in FTAS, which consisted of about 15% of the total applied radioactivity. (The TCA precipitable radioactivity of labeled charges of FTAS amounted to an average of 85%.) The operation itself may have delayed the maximum excretion of free, non-protein-bound iodine to the 2nd postoperative day.

The second peak of ^{125}I excretion between the 3rd and 5th postoperative days in animals of groups G and H coincided with the resorption of the fibrin clot by macrophages (group I) (Fig. 5) and may thus be derived from small iodinated fibrin fragments or from iodine freed in the process of clot organization. These data suggest that the fibrin clot was not dissolved until the 3rd day and could therefore provide hemostasis during this critical time. The protracted secretion of radioactivity after the 5th postoperative day in animals of group H may be caused by slow release of fibrinolytic fragments from macrophages (Fig. 6). We excluded the possibility that the collagen fleece interfered with the resorption of FTAS by finding that urinary iodine excretion was identical in groups G and H.

Wound healing after clot formation is initiated by emigration of granulocytes, macrophages and by capillary sprouting. (The Importance of Fibrin in Wound Repair, see G. Schlag et al.). Bösch [2] claimed that FTAS on a porous carrier accelerated wound healing in bone when compared with controls in which FTAS had not been used. Since proper controls for our kidney resections could not be obtained – because the untreated kidney wound would cause recurrent severe hemorrhage [3] and because mechanical damage of the kidney tissue may also cause conditions different from those caused by surgical treatment – no conclusions concerning the speed of wound healing in our experimental system could be drawn. In addition cyanoacrylate tissue adhesive cannot be used as a control because of its cytotoxic activity. The results of wound healing in rats after partial kidney resection and application of FTAS are similar to studies of wound healing in the rabbit's ear with physiological fibrin concentrations [7]. The use of homologous fibrinogen cryoprecipitate excluded any possible influence of foreign protein on hemostasis. Eosinophilic infiltration as a sign of allergic reaction [10] was not observed.

The wedge-shaped ischemic necroses (3/32) were due to the division at operation of a functional end-artery.

Comparing the results of the in vivo experiments with the data on the physiological wound healing process contained in the chapter "The Importance of Fibrin in Wound Repair" by G. Schlag et al., we find absolute agreement between the physiological process and the application of Tissucol as regards the time of wound healing, the inflammatory phase, and fibroplasia. The highly concentrated fibrin clot with addition of proteinase inhibitors in no way impedes the influx of polymorphonuclear granulocytes and macrophages and thus cellular fibrin degradation. Connec-

tive tissue proliferation and formation of granulation tissue are not influenced either. The excessive increase of proteinase inhibitor concentrations in the clot prevents the urokinase plasminogen-induced lysis of the fibrin clot in the in vitro test, although only a short-term delay in cellular degradation by proteinase inhibitors up to a maximum concentration of 1500 KIU aprotinin is possible. Taking into consideration that even short-term prolongation of fibrin stability induces increased influx of macrophages and thus fibroblasts and collagen fibers, it should be a clinical consequence of this examination to vary the addition of fibrinolysis inhibitors according to the clinical field of application of the fibrin sealant.

If atraumatic tissue synthesis has priority, such as in microvascular anastomoses and nerve anastomoses, no aprotinin should be added, thus avoiding unnecessary connective tissue proliferation, collagen fiber formation, and shrinking cicatrization. Sealing of parenchymatous organs such as the kidney, liver, and spleen certainly requires safe long-term hemostasis, justifying the application of aprotinin (1500 KIU/ml clot) in the fibrin clot.

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Preliminary Results of a Randomized Controlled Study on the Risk of Hepatitis Transmission of a Two-Component Fibrin Sealant (Tissucol/Tisseel)

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Key words: two-component fibrin sealant, hepatitis, ALT, gamma-GT, cerclage, conization

Abstract

A hundred patients who were to undergo cerclage or conization were entered into the study, being assigned to either group A or B on a random basis, irrespective of the type of surgery planned. Group A received conventional surgery plus two-component fibrin sealant, group B received conventional surgery alone.

The objectives of the study were to demonstrate the efficacy of fibrin sealant as a sealing adjunct in cerclage and as an aid to wound healing in conization. A further objective was to evaluate the risk of hepatitis B and hepatitis non-A/non-B transmission through fibrin sealant. Efficacy results are published elsewhere; here data are presented only on the risk of viral hepatitis transmission.

Of the 100 patients who had entered the study, 69 had a sufficient number of blood samples taken to qualify for evaluation of the hepatitis risk (group A: $n = 31$; group B: $n = 38$). None of the patients in either group contracted hepatitis B or non-A/non-B.

Introduction

Tisseel or Tissucol is a biological two-component fibrin sealant which is used to achieve hemostasis, to seal leakages, to glue tissue, or to support sutures. Tisseel has been found also to enhance wound healing [1]. The freeze-dried product is manufactured from pooled plasma of selected donors. Donors of this plasma are tested at every donation for HBs antigenemia using radioimmunoassay. To reduce the risk of nonA/non-B hepatitis transmission [2, 3, 4], only plasma of alanine aminotransferase (ALT) levels below 25 U/liter (reaction temperature 25°C, optimized method; [5] are used for manufacturing fibrin sealant. Thus far, two prospective, nonrandomized studies have been published investigating the risk of hepatitis transmission associated with the use of fibrin sealant. One such study was conducted in general surgery [6], the other in ENT surgery [7]. In neither of the two studies has a case of hepatitis B been seen that might have been attributable to the use of fibrin sealant. In a substudy to the ENT study, two groups of ten patients each were also tested for transaminase at biweekly intervals for a total period of 8 months. In none of these patients could an increase in ALT beyond 50 U/liter be seen.

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The study which is described below was a prospective, randomized, controlled study investigating the efficacy of fibrin sealant as an adjunct to conventional surgical techniques employed for cerclage and conization in obstetrics and gynecology, respectively. In its context patients were monitored for potential virus hepatitis associated with its use.

Material and Methods

Patient Group Assignment Procedure

Patients were assigned to group A or B by computer random numbers, irrespective of whether they were to undergo cerclage or conization. Patients in group A received two-component fibrin sealant in addition to conventional surgical methods; patients in group B served as a control and received conventional surgical treatment only. Cerclage was performed around the 16th week of pregnancy.

When patients were entered, they received envelopes bearing consecutive numbers which assigned them to either group A or B. This made it impossible for the surgeon to give preference to one of the two methods (conventional surgery alone or conventional surgery plus fibrin sealant). Each patient consented to entering the study in writing.

Dosage

All patients in group A were treated with 1 ml of fibrin sealant, which corresponds to approx. 100 mg fibrinogen. One lot of product was used.

Laboratory Tests for Viral Hepatitis

Blood samples were taken immediately before surgery, on the 3rd, 7th, and 14th days postsurgery, and 4, 6, 8, 10, 12 and 24 weeks postsurgery. Shorter intervals, it was felt, would have led to poor patient compliance. From each sample of whole blood, serum was obtained by routine hospital methods. Two milliliters of each serum sample was deep-frozen to provide documentation samples and the rest was tested for ALT, γ-GT, HBsAg, and HBsAb. If a sample proved positive for HBsAg or HBsAb, further tests were done to clarify the patient status, including tests for HBcAb, HBeAg, and HBeAb.

ALT was determined using commercially available reagent kits (Boehringer Mannheim; GPT optimized) at a reaction temperature of 25°C (recommendation of the German Society for Clinical Chemistry) [5]. For internal quality control three commercially available control sera were used (Monitrol I and II, Merz and Dade; and Precinorm U, Boehringer Mannheim) along with an in-house serum. The controls were tested at the beginning and end of each test series. Kinetics were measured using a Beckman spectral photometer (Model 25) and printer. Samples were measured manually and extinctions were printed at 60s. intervals. Extinction

differences per minute (△ U/min) were converted into U/liter using an extinction coefficient of 1756. Measuring time: 3 min; wavelength: Hg 365 nm. The manufacturer defines the normal range for women to be ≤ 17 U/liter [8, 9].

γ-GT was determined using commercially available kits by Boehringer Mannheim (Monotest Gamma-GT new) [10]. Reaction temperature: 25°C; measuring time: 3 min; print out of extinctions every 60 s.; wavelength: Hg 405 nm. Extinction differences (△ U/min) were converted into U/liter using an extinction coefficient of 1158. The manufacturer defines the normal range for women as between 4 and 18 U/liter [11]. The internal quality control of γ-GT was performed in analogy to ALT determination.

HBsAg and HBsAb were determined using RIA-QUICK (Immuno AG, Vienna), AUSRIA, and AUSAB (Abbott). Determination of HBcAb, HBeAg and HBeAb was performed using CORZYME and HBe-EIA (ELISA Method, Abbott). Four in-house quality control sera which were calibrated against international standards were used to determine HBsAg and HBsAb. For HBsAg determination the internal quality control sera were calibrated against the HBs Reference Antigen (subtypes *ad* and *ay*) of the Paul-Ehrlich-Institute, Frankfurt/Main (concentration 50 000 U/ml), and the British Reference Preparation of Hepatitis B Surface Antigen (1st British Reference Preparation established 1982 – concentration 100 Units by definition) [12]. The limit of detection for HBsAg was also tested using the standard of the Paul-Ehrlich-Institute and was found to be 0.5 ng of HBsAg/ml. For quality control of HBsAb determination the HBV-Referenzserum (IgG) of the Paul-Ehrlich-Institute Frankfurt/Main was used in a concentration of 25 IU/vial and the WHO Anti-Hepatitis B Immunoglobulin Standard, 1st Reference Preparation 1977, lot 26.1.77, in a concentration of 50 IU anti-hepatitis B immune globulin [13, 16]. HBsAg-positive results were confirmed using the inhibition test in the radioimmunoassay. HBsAb-positive findings having a concentration of ≤ 10 mU/ml were considered negative.

Results

Altogether 100 patients (group A, $n = 50$; group B, $n = 50$) were recruited into the study; 72 underwent cerclage, 28 conization (Table 1).

An evaluation of the efficacy of fibrin sealant in the treatment of cerclage and conization has been published elsewhere. In the following only the hepatitis risk associated with fibrin sealant is discussed. To evaluate this risk, only patients were

Table 1. Patient sample and group assignment

Group	Treatment	*n*
A (with Fibrin Sealant)	Cerclage	37
A (with Fibrin Sealant)	Conization	13
B (without Fibrin Sealant)	Cerclage	35
B (without Fibrin Sealant)	Conization	15
	Total	100

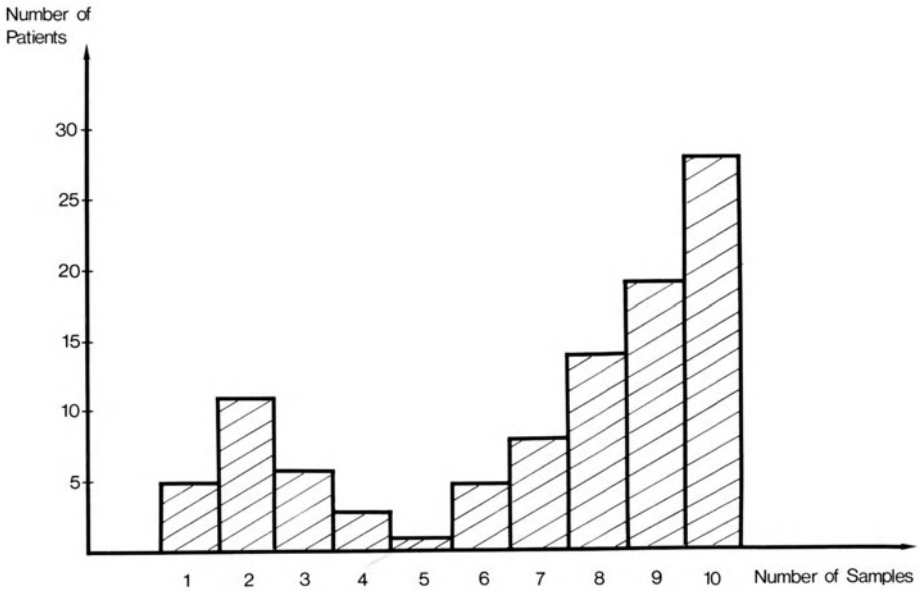

Fig. 1. Frequency distribution of patients and blood samples

used from whom at least seven consecutive blood samples (over a period of at least 10 weeks postsurgery) were available. Of the 100 patients in the study only 69 presented for blood sampling seven times or more (Fig. 1). Table 2 gives the proportion of patients who had at least seven blood samples taken and qualified for evaluation of the hepatitis risk and those who did not. As can be seen, 31 patients (23 cerclage and 8 conization) qualified in group A and 38 patients (29 cerclage and 9 conization) in group B. The percentage of patients undergoing conization in groups A and B was about the same (62% and 60%, resp.). In group B the percentage of patients undergoing cerclage (83%) was higher than in group A (62%).

Table 2. Proportions of patients qualifying and not qualifying for the evaluation of hepatitis transmission

	Nonevaluable patients	Evaluable patients	Sum (100%)
A/cerclage	14 (38%)	23 (62%)	37
A/conization	5 (38%)	8 (62%)	13
B/cerclage	6 (17%)	29 (83%)	35
B/conization	6 (40%)	9 (60%)	15
Total	31	69	100

Hepatitis B Markers

From among the 69 patients who had at least seven consecutive blood samples taken, one had to be excluded from evaluation because of receiving hepatitis B vaccination in the 4th, 8th and 12th week post fibrin sealant application.

Of the remaining 68 patients, two tested positive for HBsAb of all blood samples taken, including the preoperative one. These patients must be considered immune to hepatitis B. In three more patients HBsAb was detected on the 2nd and 7th postoperative days in concentrations below 15 mU/ml. Two of these three patients tested negative for HBsAb on all other blood samples. In one patient in group B who underwent cerclage, HBsAb findings were positive, in a concentration of as low as 13 mU/ml 6 months postsurgery. Two of the patients tested positive for HBsAg on all samples, including the preoperative sample.

Hepatitis Non-A/Non-B Markers

By definition, non-A/non-B hepatitis can only be suspected if ALT is increased postoperatively to 2.5 times the upper limit of normal. In all, 12 ALT increases (ALT > 20 U/liter) were detected, eight in group A and four in group B. Two patients (both in group B) only had slightly increased values initially (in one case 39 U/liter preoperatively, followed by normal findings on all postoperative samples; in another case a pathological 49 U/liter on the preoperative sample, which normalized in the course of the subsequent 2 weeks). Two more patients in group B had slightly increased ALT values without hepatitis B markers 6 months postoperatively (41 and 46 U/liter). One patient in each group had increased ALT values in postoperative weeks 6 and 8 (46 and 40 U/liter, resp.) without hepatitis B markers. None of the patients had clinical symptoms of non-A/non-B hepatitis.

In addition to ALT, γ-GT was monitored as an indicator of the possible presence of non-A/non-B hepatitis. Nine increased γ-GT values were found in all (six in group A, three in group B). The increased γ-GT results were often borderline. One patient in each group had preoperatively increased γ-GT (114 and 41 U/liter, resp.) which returned to normal in the course of the observation period in one patient and dropped to half the initial value in the other. One more patient in group A had a one-time increase in γ-GT of 46 U/liter 10 weeks postoperatively.

Discussion

The main ingredient of two-component fibrin sealant is fibrinogen, which is present in a concentration ranging from 70 to 110 mg/ml. Products made from human plasma are known to have the potential of transmitting viral hepatitis, unless special donor screening methods are used and/or products are subjected to a virus inactivation procedure. To exclude hepatitis B, donations have been tested for HBsAg before such plasma is used for processing into plasma derivatives ever since third generation test methods became available (radioimmunoassy and/or ELISA). This measure dramatically reduced hepatitis B transmission. Nevertheless, a high percen-

tage (up to 98%) of hemophiliacs have been shown to have hepatitis B markers [14]. In addition, chimpanzee trials have shown that infectivity of some plasmas persists despite negative HBsAg findings in the radioimmunoassay, rendering hepatitis B transmission possible [15].

The difference between the infection titer and HBsAg titer in the radioimmunoassay may be as large as two or three orders of magnitude. This means that plasmas testing negative for HBsAg can still transmit hepatitis B.

Probably, there is a relation between dosage and infectivity. As Tabor [16] has demonstrated, hepatitis B virus infectivity which might still be present in such plasmas or plasma derivatives may be neutralized by hepatitis B immunoglobulin. Therefore, addition of anti-HBs either during or after the manufacture of such products is a practical approach to prevent hepatitis B [17]. A similar immunologic neutralization of non-A/non-B hepatitis agent is not possible because neither the agent nor the protective antibody has been identified so far.

To reduce the risk of non-A/non-B hepatitis transmission, the manufacturer of fibrin sealant tests all donations of plasma for ALT levels. As early as 4 years ago serum alanine aminotransferase in donors could be shown to have a correlation with the risk of non-A/non-B hepatitis transmission [2, 3, 4]. However, experience has shown that rigorous quality control criteria – every donation with ALT levels $\geq$ 25 U/liter (25°C reaction temperature) is discarded and excluded from processing – reduce non-A/non-B hepatitis transmission, but do not eliminate it completely. The mechanism involved in the transmission of non-A/non-B hepatitis by fibrinogen or fibrin sealant was investigated in 1980 [18]. At that time, one lot of fibrinogen triggered non-A/non-B hepatitis in two patients and one patient developed chronically persisting hepatitis 2 years after the onset of the acute phase of the disease. The same lot of fibrinogen was injected intravenously into a chimpanzee in a concentration of 200 mg and produced typical non-A/non-B hepatitis with ultrastructural changes of the hepatocytes [19]. The chimpanzee developed an ALT level of 55 Karmen U/ml (five times the baseline 11 weeks after the intravenous administration of that fibrinogen lot). Two milliliters of pooled serum from samples drawn from that chimpanzee in weeks 4–10 postinoculation were given to another chimpanzee by the intravenous route. A typical non-A/non-B hepatitis developed in that chimpanzee 8 weeks postinoculation with that serum pool, manifesting itself in ALT increases of 4–5 times the baseline. In another study [20] a young chimpanzee was inoculated with ~100 mg of fibrinogen intravenously. The chimpanzee developed an ALT increase to 227 U/liter after a 16-week incubation period, with light microscopic and ultrastructural changes typical of non-A/non-B hepatitis. The two studies have shown that concentrations ranging from 100 to 200 mg may trigger non-A/non-B hepatitis if given intravenously. It must be borne in mind, however, that fibrinogen is not given intravenously when fibrin sealant is applied, but that clottable protein is transferred into a viscid solution which solidifies rapidly into a rubberlike mass after the addition of aprotinin, thrombin, and calcium chloride. The course of this solidification bears analogy with the physiological process of coagulation. For that reason, it is not likely that fibrinogen enters the circulation. It was the aim of this study to show that fibrinogen given in concentrations which produce non-A/non-B hepatitis if given intravenously, do not transmit non-A/non-B hepatitis if applied in the routine product combination.

Evaluation of the Risk of Hepatitis B Transmission

A prospective study on the viral transmission of hepatitis B carried out from 1979 to 1981 in the same department has shown 23 (or 0.52%) of 4400 pregnant women who were examined consecutively for the presence of hepatitis B markers to be antigen carriers [21]. The prevalence of HBsAg-positive pregnant women is determined by the ethnic composition of a patient population, particularly in countries with a low incidence of HBsAg (22). Sixty-five percent of the antigen carriers identified in the above study came from Southern Europe, Turkey, and the Philippines. The frequency of HBsAg carriers in the 3 year study varied widely. The small patient sample in the fibrin sealant study (68 evaluable patients out of 100) explains the nonrepresentative frequency of HBsAg and HBsAb in this group of women. Since in all samples (including the one taken preoperatively) HBsAb could be identified in only two patients, the percentage of patients considered to be immune to hepatitis B is too low, while the percentage of HBsAg carriers (2 of 68) is too high. One of the HBsAg carriers was a 29-year-old woman with an incompetence of the cervical canal who had a cerclage performed in the 17th week of gestation. HBs antigenemia in patients with normal liver function have been known for well over 4 years. The second case was a 33-year-old woman who had the same problem and the same intervention performed in the 15th week of gestation and gave birth in the 41st week. This patient had no history of HBs antigenemia and none of her relatives had hepatitis B.

The HBsAb which was detected in three patients on the 2nd and 7th postoperative days in concentrations of $\leq$ 15 mU/ml could not be clearly confirmed to have been HBsAb by inhibition. The concentrations were too low. HBcAb could not be detected. This suggests the HBsAb involved to probably have been a nonspecific one [23, 24].

In only one patient (group B) could HBsAb be detected 6 months after cerclage had been performed, in a concentration of 13 mU/ml. Since HBcAb was absent, this could not be considered a seroconversion. The results, therefore, suggest that fibrin sealant does not transmit hepatitis B, since none of the patients underwent hepatitis B infection serologically or clinically within the 6-month observation period.

Evaluation of the Risk of Non-A/Non-B Hepatitis Transmission

Since at the present time no serological test methods are available for the detection of non-A/non-B hepatitis virus(es) [25], the non-A/non-B hepatitis risk can only be assessed based on biochemical tests such as ALT or to a certain extent γ-GT. Some time ago determination of reverse transcriptase was described as an indicator of non-A/non-B hepatitis[26]. The sera available to us cannot be used for this determination, since this requires the plasma or serum samples to be deep-frozen at −70°C immediately after they are taken, which was not done with the documentation samples collected. If typical clinical and biochemical findings were present, non-A/non-B hepatitis could only be diagnosed by exclusion of other forms of hepatitis, including cytomegaly and Epstein-Barr. Liver biopsies could not be taken for ethical reasons. Therefore, the risk of non-A/non-B hepatitis transmission was assessed

based on elevated ALT and γ-GT levels. Numerous chimpanzee studies have shown that increases in ALT or γ-GT values beyond 2.5 times the baseline or normal upper limit are indicators of non-A/non-B hepatitis.

For well over a decade, statistically significant correlations have been known to exist among age, weight, sex, and enzyme activities. A correlation between weights and ALT levels is more markedly present in men than women. In women, on the other hand, age plays a more important role in younger women (below 30). The normal range of ALT values does not exceed 10 U/liter (0.95 quantile). In women between 30 and 40 years of age, the normal range lies between 5 and 21 U/liter with a median of 9 U/liter [9]. Studies on the normal range of ALT during pregnancy (where higher enzyme activities must in principle be expected) have not been done. The small patient sample did not allow stratification by age, body weight, or weeks of gestation if cerclage was involved. For all of the above reasons, the upper limit of the normal range was defined to be 20 U/liter and the limit beyond which non-A/non-B hepatitis was present was defined to be 50 U/liter (2.5 times the upper limit of normal). γ-GT levels were interpreted analogously. However, little is known about the correlation between γ-GT, age, weight, and sex.

Since γ-GT levels are also expected to be slightly higher during pregnancy, the upper limit of normal was again taken to be 20 U/liter and the limit for non-A/non-B hepatitis 50 U/liter (2.5 times the upper limit of normal). The slightly increased ALT levels of 41 and 46 U/liter 6 months postoperatively in the two patients in group B cannot be correlated with non-A/non-B hepatitis. In one patient ALT levels were increased 5 days before delivery of twins. In the other the increased enzyme activity showed 2.5 months postpartum.

The increased ALT levels of 46 and 40 U/liter in two patients, one in group A, one in group B, are below the defined limit for non-A/non-B hepatitis. The increased γ-GT value of 46 U/liter 10 weeks postoperatively in one patient (group A) cannot be interpreted as indicative of non-A/non-B hepatitis either.

Conclusions

Two-component fibrin sealant does not transmit hepatitis B or non-A/non-B hepatitis. Of 69 patients who qualified for evaluation of viral hepatitis transmission out of 100 entered into a randomized controlled study, none had hepatitis B, seroconversion, or clinically or biochemically manifest non-A/non-B hepatitis.

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II. Plastic Surgery

The Use of Fibrin Sealant in Patients with Rhinophyma

O. STAINDL

Key words: Rhinophyma, fibrin sealant, factor XIII, wound healing

Abstract

Rhinophyma is one of those conditions wich may result in gross and grotesque nasal deformities and disfigurements. The treatment of rhinophyma is invariably surgical and consists in the removal of the masses in order to restore a normal nasal shape in aesthetic terms.

Our own technique for management, using a combined surgical and glueing procedure, is described in the present paper. Major tuberous masses of the nose are resected in layers with disposable razorblade. For wound care we spray a thick film of fibrin sealant generously across the entire wound surface.

The advantages, offered by this method described are:

- safe hemostasis
- rapid wound healing
- reduced length of hospitalization
- excellent aesthetic results.

Introduction

The midface plays a critical role in the individual's physiognomy, which reflects his or her personality. Its most prominent part, the nose, is of particular importance. Major congenital or acquired abnormalities of nasal shape and structure are not only determinant of a person's facial expression, they also affect his or her emotional development and social behavior.

Rhinophyma is one of those conditions which may, at times, result in gross and grotesque nasal deformities and disfigurements. This is what has fascinated caricaturists and artists throughout the centuries. Among the many classical paintings featuring a person with rhinophyma, Domenico Ghirlandaio's (1449-1494) portrait of a grandfather and grandson, currently in the collection of the Louvre, is no doubt the most famous [3] (Fig. 1).

Although the condition was known to Hippocrates and repeatedly mentioned in the writings of early physicians, the term "rhinophyma" was introduced late, i. e., by Ferdinand von Hebra (1816-1880), who used it to describe the third stage of nasal acne rosacea. This notion was upheld for a long time; but in recent years rhinophyma became accepted as an independent disease entity of unknown pathogenesis

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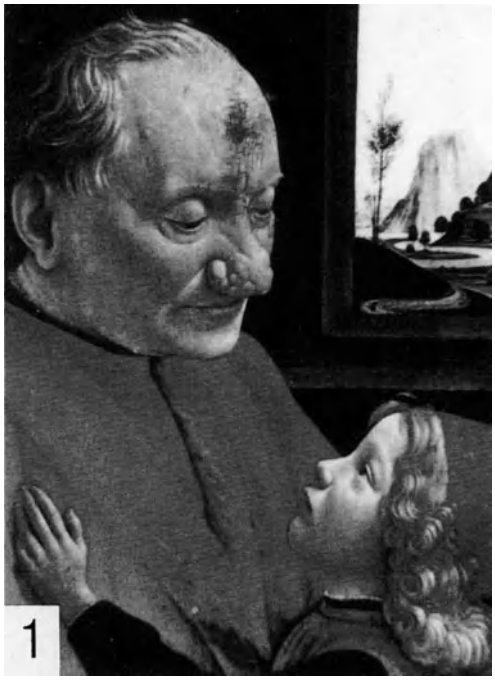

Fig. 1. Domenico Ghirlandaio (1449-1494): "Grandfather with his grandchild" (Paris, Louvre)

which, though commonly encountered in patients with both seborrhea and acne rosacea, need not necessarily be associated with these two conditions [9] (Fig. 2).

Paradoxically, rhinophyma is 12 to 20 times more common in males than in females, while rosacea affects females 3 times as often as males, as Fára [6] reported. Many different pathogenetic factors have been incriminated, including impaired intestinal function, vitamin deficiencies (B,C,E), hormonal disorders, angioneurosis, exogenous stimuli, poor skin hygiene and alcohol abuse. Both in the vernacular

Fig. 2. Ferdinand von Hebra 1816-1880)

and in medical jargon, the common association of rhinophyma with alcoholism has given rise to such terms as "whiskey nose," "rum nose," "brandy nose," "Potato nose" and "copper nose" [4].

Pathology

Initially, rhinophyma is characterized by slowly progressive hyperplasia of the subcutaneous connective tissue and vessels. In the further course tuberous, indolent, firm pseudotumors of the skin develop. These are predominantly localized in the lower third of the nose, but may also occur on the forehead, the cheeks, the chin (mentophyma) and, rarely, the ears (otophyma).

The pseudotumors reflect slowly progressive hyperplasia of the sebaceous glands. Depending on the most prominent tissue component, rhinophyma may be fibro-angiomatous or glandulotuberous in nature [10].

Freeman [7] distinguished five variants by the severity of the condition: These range from a fibrovascular initial stage to a grossly tuberous stage. Histologically, massive sebaceous gland hyperplasia associated with newly formed connective tissue and vessels is prominent. The nose's supportive structures, i.e., the nasal cartilages and bones, are unaffected [4]. Although basically a benign disease, rhinophyma is often found to give rise to spinocellular carcinoma and basalioma [1].

Management

Management is invariably surgical and consists in the removal of the masses to restore a normal nasal shape in terms of aesthetic rehabilitation. Various procedures have been proposed. According to Friedrich (1967) [8], these include:

1. Excision of rhinophymatous masses together with the overlying skin and direct suture of the wound edges in analogy to the method described by Dieffenbach in 1945
2. Total removal and closure of the resultant defect by transposition of skin
3. Subcutaneous excision [4]
4. Piecemeal removal with a knife or razor in layers ("decortication") with spontaneous re-epithelialization from the remaining skin islands
5. Electroabrasion with cutting diathermy loops or knives (this may be associated with damage to the underlying cartilage)
6. Abrasion of the entire nasal skin and coverage of the defect with split-thickness or full-thickness skin grafts
7. Dermabrasion
8. Cryosurgery with liquid nitrogen at $-35°C$ [11]

We have come to use a multicomponent approach combining several of the above procedures. Considering that rhinophyma is the endstage of a chronic inflammatory process rather than a true neoplasm, we feel that the diseased skin need not be radically removed, because hyperplasia tends to originate from the topmost layers, leaving those in the depth more or less unaffected. Ardouin [3] was right in saying that "the normal nose was hidden underneath the rhinophyma." Uncovering it

without removing the entire skin down to the nasal cartilage is, therefore, all that needs to be done. The wound will eventually be re-epithelialized spontaneously from the abundant sebaceous gland ducts. Consequently, split-thickness or full-thickness skin grafting appears to be unnecessary. In most cases the cosmetic results obtained are unsatisfactory anyway, because the graft's color usually does not perfectly match that of the surrounding facial skin [2].

To support the tip of the nose the surgeon's index finger is introduced into the patient's nostril. With a wide-bladed knife major tuberous masses are resected in layers from the top downwards. Once the nose has been grossly restored to its original shape, it is modeled to perfection by scraping the excessive tissue away with a one-way razor. This helps to prevent irregularities in contour and provides for a smooth transition to the skin of the cheek (Fig. 3).

We do not consider electrosurgical resection a useful alternative, because uncontrollable necrosis in the depth of the tissue may eventually result in a discontinuous nasal contour. Diffuse bleeding from the operative field, which is usually profuse, is controlled with cold compresses soaked in hydrogen peroxide. Electrocoagulation of one or the other vessel with a bipolar coagulator is only exceptionally needed.

Compression dressings of wide-meshed gauze have been recommended for wound care [9]. In our experience, these tend to stick to the wound so that, when dressings are changed, crusts are torn off and the wound bleeds again. This has prompted us to spread a thick film of fibrin sealant generously across the entire wound surface. The advantages of fibrin sealant are twofold: It provides for meticulous control of diffuse bleeding and serves as a "physiological" epithelial dressing. In addition, fibrin is one of the fundamental elements involved in tissue healing. As fibrin sealant also contains factor XIII, fibroblast ingrowth and early re-epithelialization are promoted. Fibrin sealant is a two-component system based on the precipitation of human fibrinogen by thrombin. The two components can be applied separately or together using a double syringe. Spraying is the optimal mode of application, because it

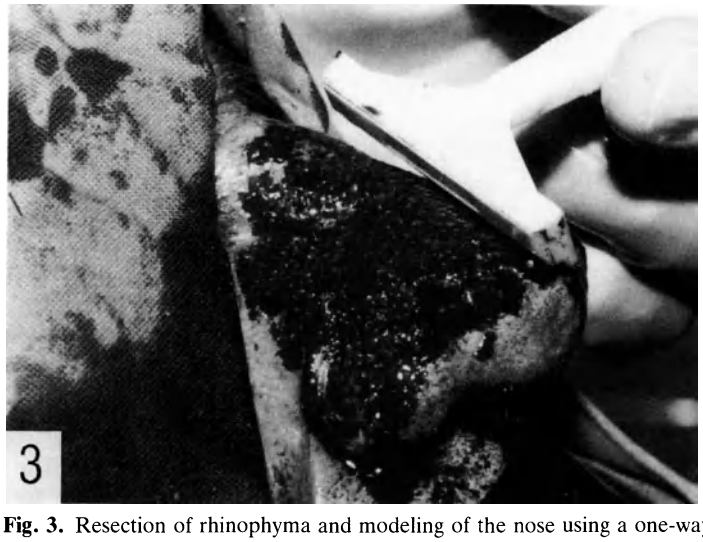

Fig. 3. Resection of rhinophyma and modeling of the nose using a one-way razor

deposits a fibrin film of uniform thickness. The originally viscoelastic fibrin clot dries gradually and can be removed after some days like a crust. In most cases the subjacent wound surface has by then been spontaneously re-epithelialized. Exceptionally, reapplication of fibrin sealant may be necessary (Figs. 4–7)

In our experience, wounds covered with fibrin sealant tend to heal much earlier than with the usual dressings and ointments; in fact, wound healing is, as a rule, complete within 5–10 days. Safe hemostasis, rapid wound healing, the resultant reduced hospitalization and the excellent aesthetic results are, in a nutshell, the advantages offered by the method described [12] (Figs. 8, 9).

Occasionally, simple resection is not sufficient for reducing nasal size and thus ensuring satisfactory aesthetic rehabilitation. But the usual methods for nasal reduction, such as remodeling of the alar and lateral cartilages, transfixion and resection of the anterior margin of the septal cartilage, removal of bone from the nasal dorsum and medial displacement of the nasal bones, are equally bound to fail in such cases. Following Freeman's concept [7], we have found wedge resection through the nasal soft parts in the anterior third including the septal cartilage and reduction of the nose by painstaking adaptation of the wound edges and suture of the mucous membrane and the cartilaginous and cutaneous structures to be a useful alternative (Figs. 10–12). It can be done about 6 months after primary rhinophyma surgery. But it should again be emphasized that this procedure should be reserved for exceptional cases. As a rule, visible scarring is minimal. If necessary, secondary dermabrasion 6 months later will improve the aesthetic results.

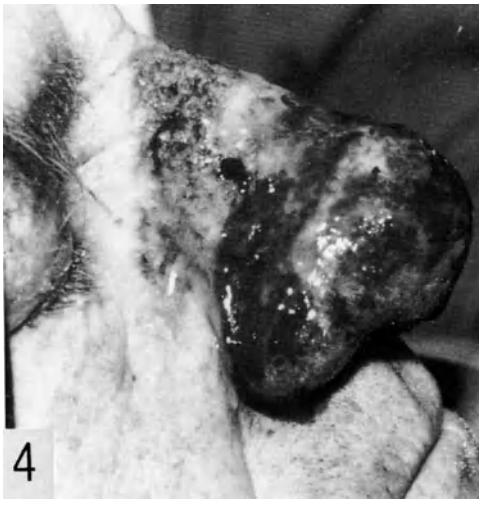

Fig. 4. The wound surface is covered with fibrin sealant (spray technique)

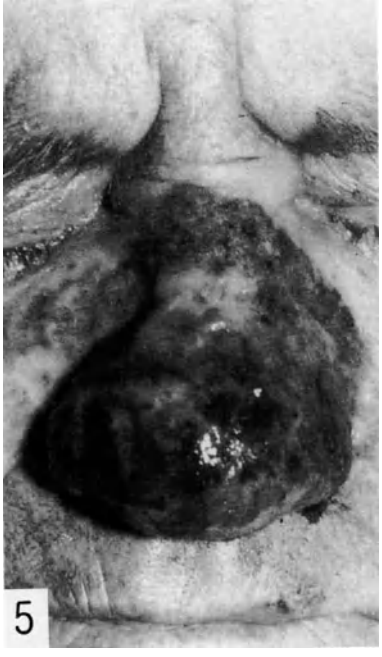

Fig. 5. Hemostasis and covering of the wound surface is completed

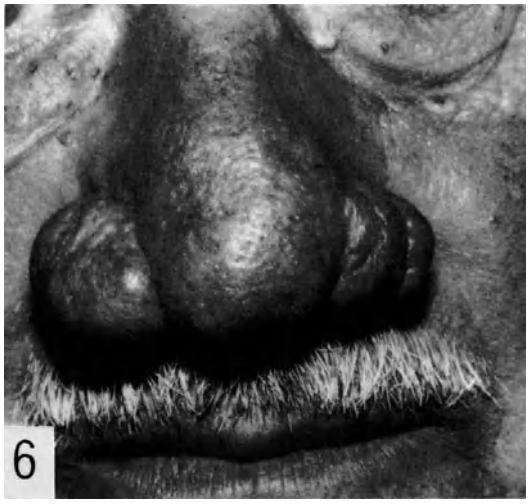

Fig. 6. Same patient as in Fig. 3–5: preoperative view

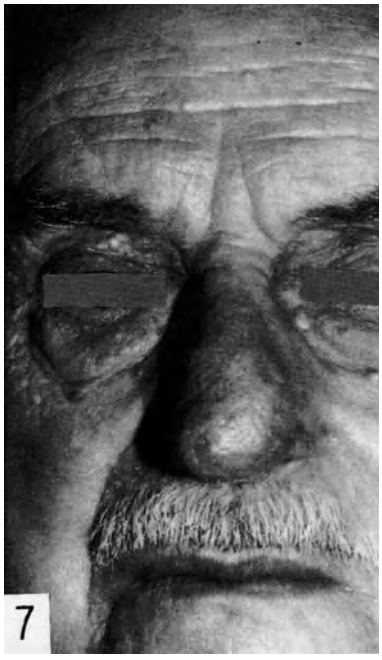

Fig. 7. Patient of Fig. 6: postoperative view

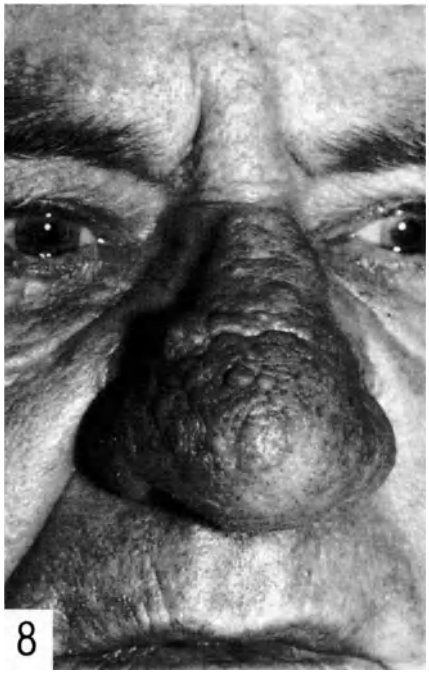

Fig. 8. Another case of rhinophyma

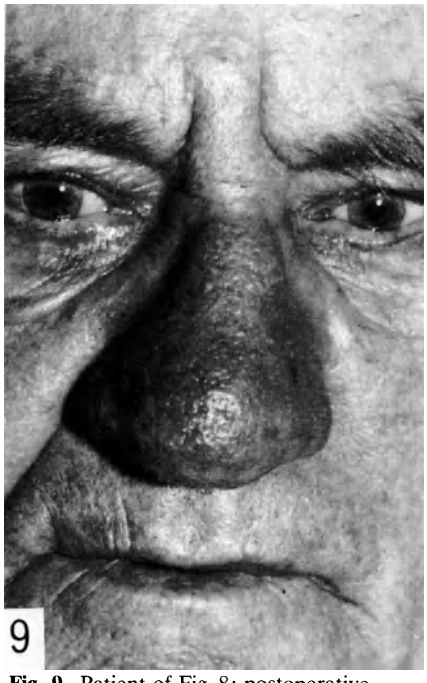

Fig. 9. Patient of Fig. 8: postoperative result after treatment described above

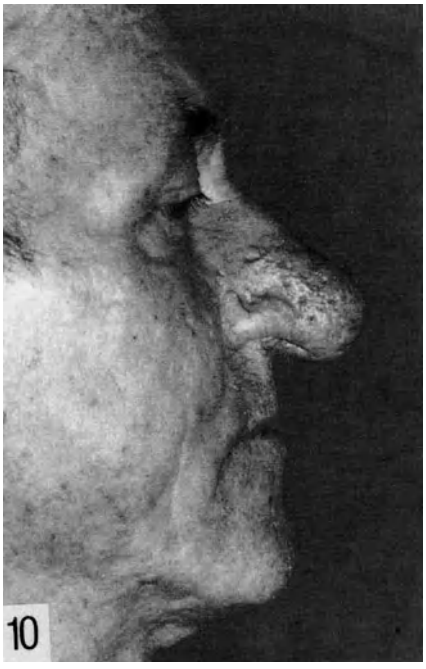

Fig. 10. Fifty-six-year-old patient with rhinophyma and excessive "longnose"

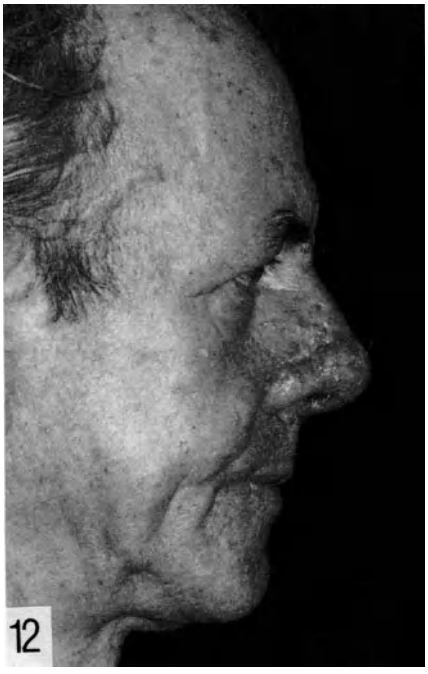

Fig. 12. Patient of Fig. 10: postoperative result

Fig. 11. Scheme of treatment: wedge resection through the nasal soft parts including the septal cartilage

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Fibrin Sealing in Plastic Surgery

A. AZZOLINI and A. BOCCHI

Key words: Plastic surgery, fibrin glue (Tissucol), tissue repair

Abstract

In plastic surgery, the advantages of using fibrin sealant (Tissucol) are due, besides the more evident immediate adhesive and haemostatic effects, to the biostimulating action on the repair of some components such as fibronectin and factor XIII. We report our personal experience of the principal clinical applications of Tissucol in plastic surgery, with particular regard to the surgery of grafts and flaps, congenital malformations, bone defects and peripheral nerves. The physiological reabsorption of fibrin glue, its excellent tissular biocompatibility and the absence of general or local side effects lead us to expect, with exact definition of the indications, more and more widespread use of this product.

With reference to the special features of plastic surgery, it is worthwhile underlining that, in addition to its adhesive and haemostatic actions, Tissucol is, as a result of some of its components such as fibronectin and factor XIII, able to exert a modulating action on the biological processes characterizing tissue repair [6, 9, 10].

When Tissucol is used in skin grafts following large resections, the reliability of its haemostatic effect and the improved guarantee of success of the graft have made it possible to increase considerably the area treated during each separate operation [2, 5, 8].

The perfect and homogeneous adherence of the grafted tissue to the recipient site, which prevents the formation of serohaematic deposits, has also made it possible to do away with clumsy compressing medications and with the total immobilization of the grafted part.

An analysis of the postoperative period has usually shown a tendency towards hypertrophic scar tissue during the first weeks; hypertrophy, however, tends to regress rapidly at such a rate that after only 6 months excellent quality and elasticity of the tegumentary cover are present.

With regards to the characteristics of the repair, a comparison between areas previously grafted without the use of fibrin glue and others re-epithelized with the aid of Tissucol may offer a reliable, method of quality comparison.

In our series we have obtained excellent results as regards tegumentation which is even both in colour and weave.

Excellent results have been obtained in the attachment of grafts, even on an uneven surface such as that resulting from the removal of a paraffinoma (Fig. 1).

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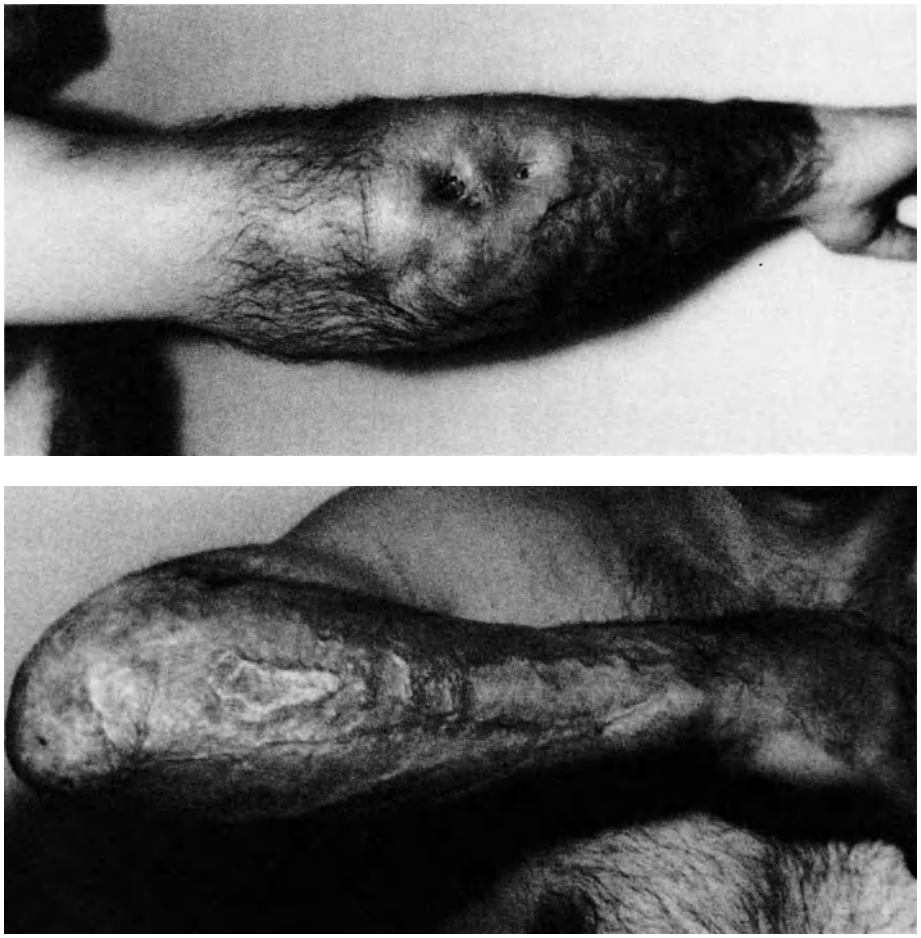


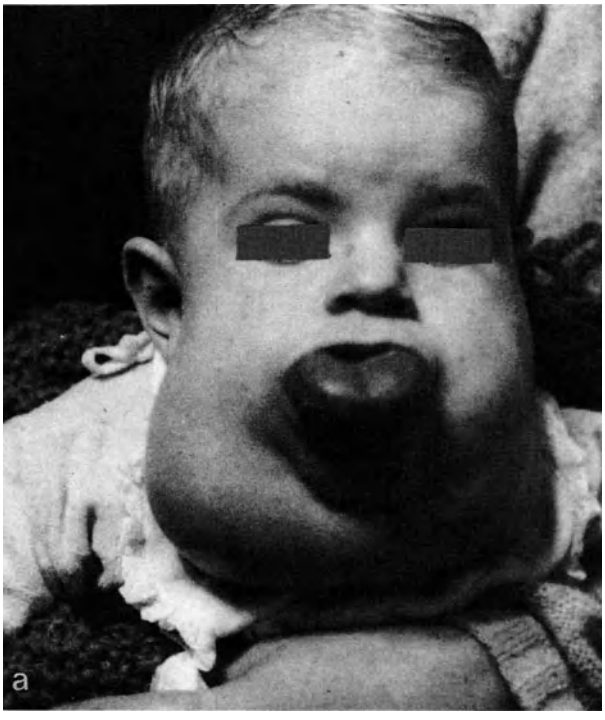
Fig. 1a, b. Graft after the removal of a paraffinoma

The effectiveness of Tissucol has also been evident in the treatment of neoplastic lesions where the demands of a radical excision often lead to the sacrifice of large areas of tissue in critical areas such as the popliteal hollow, where the absence of retraction can be observed in our cases several months after the operation of the face, where the involvement of bone structure may demand such wide demolition that haemostasis of the remaining cavity and external repairs become very difficult.

In skin flap surgery, fibrin glue guarantees complete adherence of the flaps to the underlying tissues, preventing the formation of empty spaces and of postoperative haematic collections, reducing complications due to infection which are further avoided by drainage becoming unnecessary [1, 7].

These characteristics make the use of fibrin glue particularly advantageous in surgical treatment of angiomas and of lymphoangiomas.

So exceptional surgical results may also be obtained in extremely serious cases such as the patient in Fig. 2, who had a gigantic lymphoangioma of the neck which, since it was causing increasing respiratory stenosis, was a serious threat to his life.



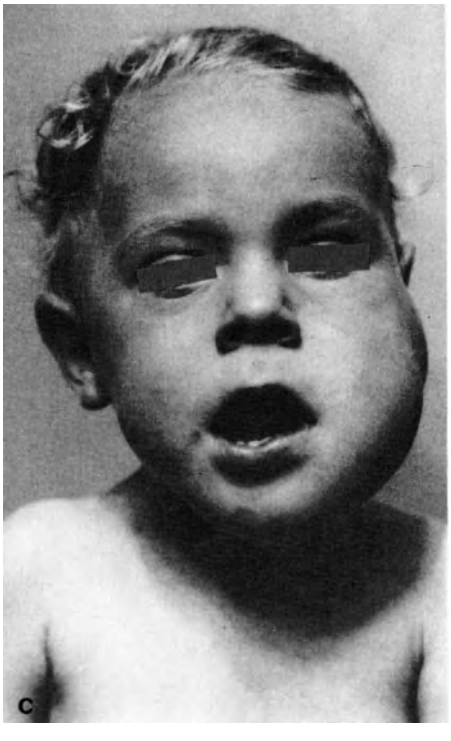


Fig. 2a–c. Patient with a gigantic lymphoangioma of the neck

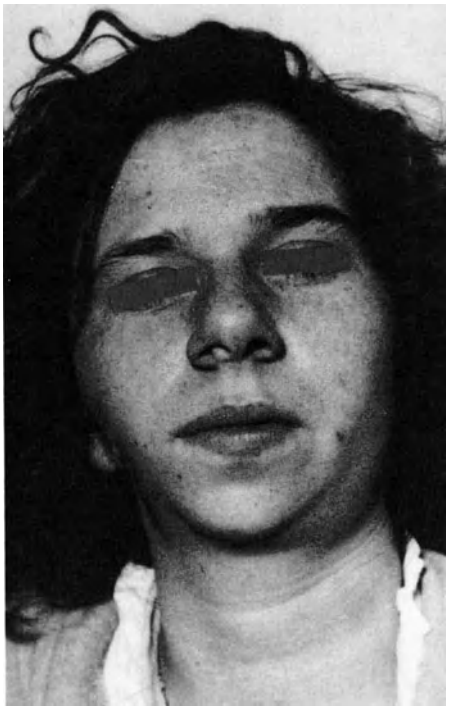


Fig. 3a

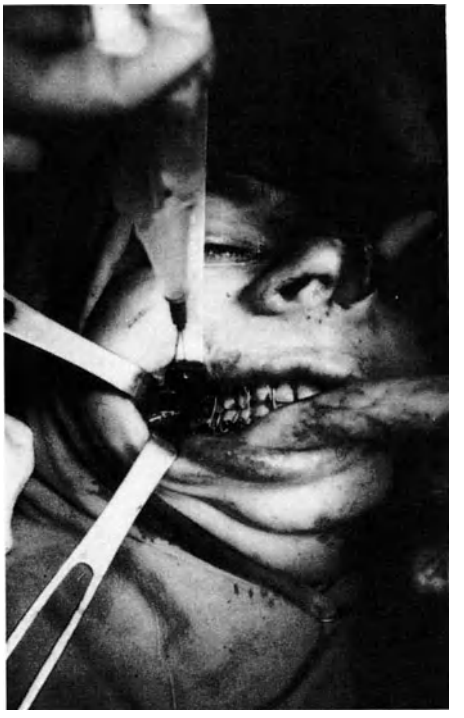


Fig. 3b

Fig. 3c

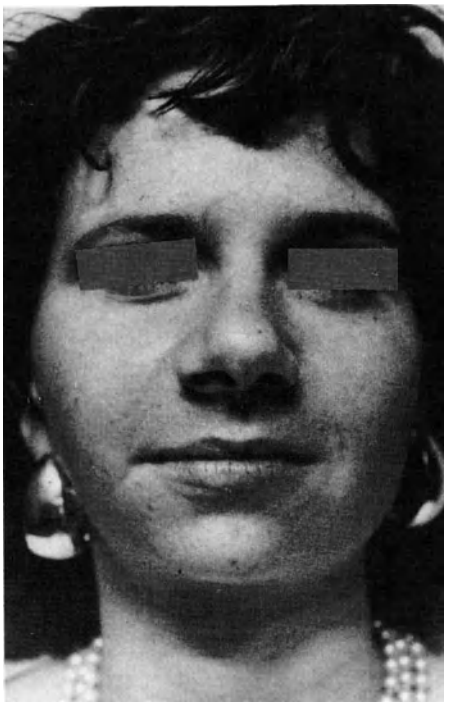
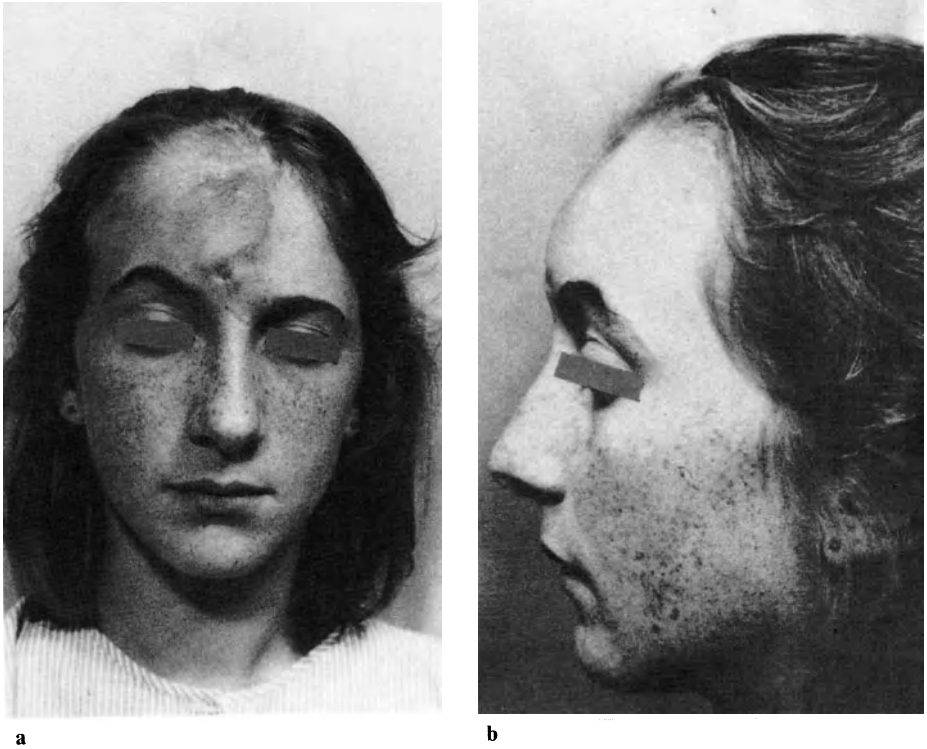


Fig. 3a–c. Patient with right-handed facial microsomy

The removal of the large lymphoangiomatic nuclei led to a radical emptying out of the neck, with decollement extending to the prevertebral space and raising of the laryngotracheal tube. In this case, in which the patient's age strictly limited the size of the haemorrhage, the use of Tissucol really made feasible an operation, whose success was also guaranteed by the total adhesion of the flaps to the underlying tissue; likewise the absence of haematomas and related infectious complications simplified the postoperative course.

In addition to its use in the reintegration and modelling of soft tissues, and here we wish also to include palatorraphies. Tissucol can also be used specifically as the sealing agent in traditional bone grafts and as a useful support to osteosynthesis in the treatment of congenital and acquired pathologies [3, 4], as in Fig. 3, which shows a case of right-handed facial microsomy in which a bilateral osteotomy of the upper maxillary according to le Fort I and a bilateral sagittal osteotomy of the jaw following Obwegesen Dal Pont, accompanied by the insertion of bone grafts drawn from the iliac crest and secured with fibrin glue to integrate and to reinforce the mobilized portions of the skeleton, were effected.

In addition, Tissucol can be used effectively to fill defects in the structure of the skeleton as in the case of Fig. 4, an angioma of the median area of the forehead. The forehead was noticeably convex owing to a thickening of the skull and the enormous development of the frontal sinus. After removal of the angiomatous skin and lifting of two lateral flaps taken on the periostal plane, the operation continued with the



a b

Fig. 4a–f. Patient with an angioma of the median area of the forehead

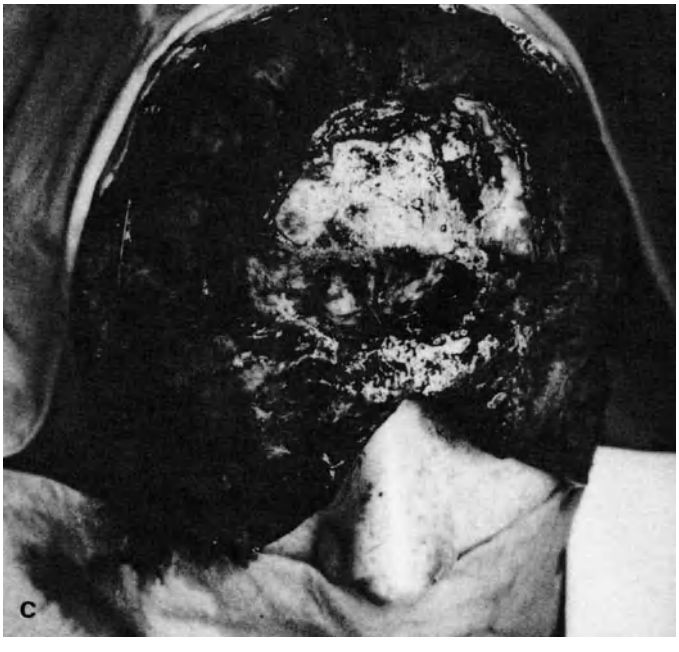


Fig. 4c

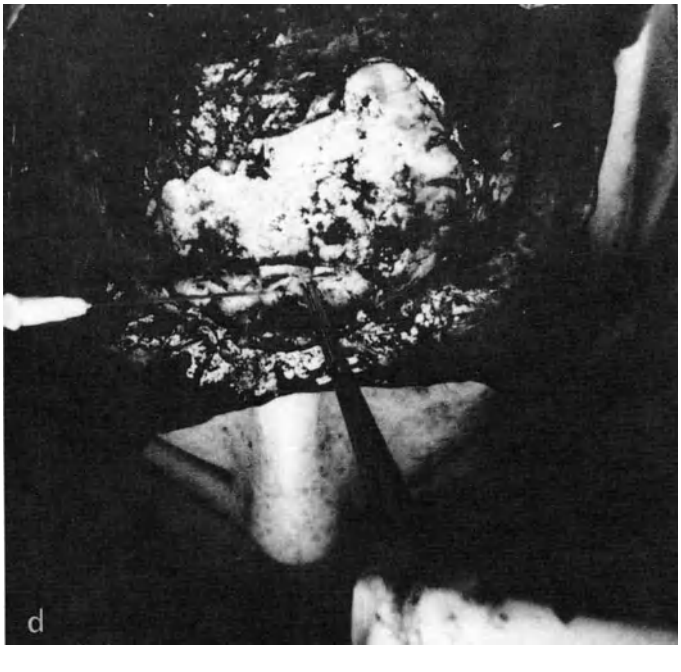


Fig. 4d

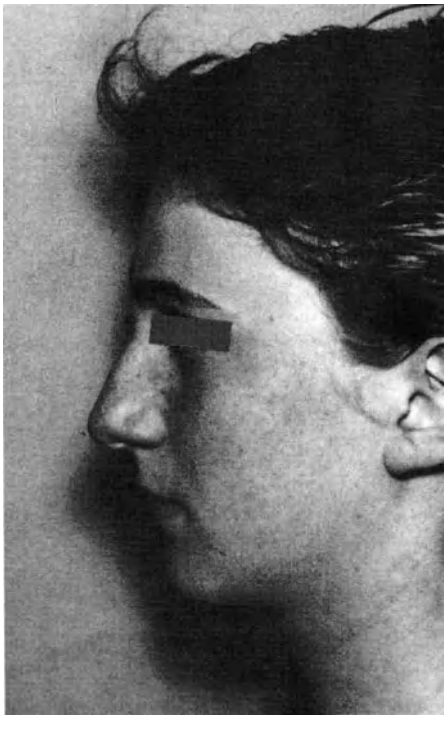


Fig. 4e

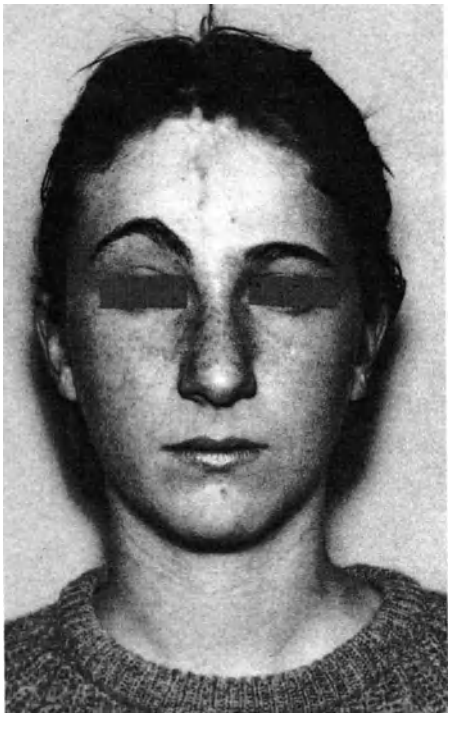


Fig. 4f

modelling of the frontal bone and emptying of the sinus. The large residual osseous cavitiy was then filled using bone chips drawn from the paring down of the skull together with fibrin glue.

The forward wall of the sinus was also reconstructed by means of an operculum obtained from the primitive wall upturned and modelled. Finally, the tegumentary reconstruction was carried out by means of the rotation and advancement of the lateral flaps.

From the clinical results we have had the opportunity of evaluating, we have gained the impression that fibrin glue may improve the course of repair processes and the final quality of scar tissue, as has been shown by the absence of retraction and the evident scar hypertrophy in reconstructions effected by skin grafts during childhood.

We may conclude that in a field of precise indications the possibilities offered by fibrin glue represent further progress in what is the natural tendency of every form of surgery: to achieve physiological and reconstructive results following antiphysiological (but unfortunately necessary) acts of demolition.

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Tissue-Adhesion Techniques in the Treatment of Extensive Postoperative Cavities and Fistulae

H.G. Bruck and E. Würinger

Key words: Tissue adhesion, fistulae, large wounds, plastic surgery

Abstract

Artificial tissue adhesion with the help of the two-component fibrin glue has proved an effective aid in the treatment of large wounds and fistulae. The selection of patients and the mode of treatment are discussed and illustrated by the histories of typical cases.

Introduction

Large wounds are not only treated by plastic surgeons, but are quite frequently sequelae of reconstructive operations (myocutaneous flaps, extensive skin-movements of local flaps). They are a necessary part of the operation and common even in aesthetic surgery (rhytidectomies and abdominal lipectomies). Haematomas, seromas and undue swelling can impede the adhesion of opposing surfaces and thus produce complications. Therefore these and various forms of fistulae, liquor (Kunze) or lymphogenic complications can pose quite a problem (Cohen at al.). Increased morbidity of the patients out of proportion with the planned operation and difficulties of primary healing are the result. Since adequate fibrinogen concentrations had been available since 1972 (Matras, Dinges et al.), tissue adhesion seemed to be a possible solution for problem cases.

Material and Methods

During the last 7 years an increasing number of cases with various expected wound-healing problems have been treated in our unit with the locally applied two-component tissue adhesive (Tissucol, Immuno). These components are:

1. Highly concentrated fibrinogen with factor XIII and other proteins, to be dissolved in Aprotinin (bovine) 3000 K/U/ml
2. Thrombin (500 IU) to be dissolved in calciumchloride (40 mg mol/ml)

When these are brought into a wound and mixed, coagulation occurs. The activated factor XIII component produces cross-links of the fibrin elements, thus favoring the cross-linking of collagen and enhancing the rigidity of the forming clot.

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However, a minimum of 5 mmol mol/ml $CaCl_2$ is necessary to produce a satisfactory rate of cross-links (Shen at al.). Aprotinin still works at a concentration of 100 IU/ml and is used at this low concentration mainly for nervegluing (Kuderna). Quick dissolution of the glue is desirable here to ease growth of fibrillae through the sutureline. We have always used thrombin 500 because we cannot see any advantage in the slow clotting rate of thrombin 4 in our field of work. To get the best out of this preparation it must be freshly prepared for each case and the two mixed components will not retain their effectiveness for more than about 4 h. During the last 7 years, tissue adhesion has been used in many suitable cases with large subcutaneous wounds and in fistulae which were difficult to treat.

The main indications are:

1. Large subcutaneous wounds
   a) Rhytidectomies
   b) Myocutaneous flaps (latissimus dorsi)
   c) Extensive skin flaps
   d) Abdominal lipectomies
   e) Flap closure of decubitus ulcers
2. Blocdissection of inguinal lymph nodes
3. Lymphatic fistulae
4. Chronic lymph "seromas"

The following are typical situations where the tissue adhesive has proved effective:

1. After latissimus dorsi myocutaneous flaps were used for breast reconstruction, large subcutaneous pockets remained on the back of the patient. Even suction drainage after meticulous haemostasis was not very effective in controlling postoperative seromas. The introduction of tissue adhesive into these cavities has remarkably reduced postoperative leakage and discomfort to the patient. Note that the opposing tissue surfaces must be firmly pressed together by external pressure for about 3–4 min to secure firm adhesion (Fig. 1).
2. Traumatic cysts had an unfortunate tendency to recur. Even after appropriate skin excisions to get rid of the surplus skin and produce adequate skin tension, the cavity remaining after excision of the capsula tended to refill with serum. The tissue adhesive proved an advantage (Fig. 2).
3. For the treatment of fistulae in the chest wall remaining after resolution of chronic empyema, extensive skin flaps are sometimes necessary. To adapt these to the rigid, very concave defect was often difficult. The use of tissue adhesive to "glue" them to the chest wall, even with some infection present, was very effective in our last three cases.
4. Another successful use of this adhesive has been in treatment of paraplegics with their various forms of decubitus ulcers and fistulae. Fibrin tissue adhesive has reduced considerably the postoperative rate of formation of fistulae and secondary cavities under covering flaps. It has become a standard adjunct to our treatment of these conditions. If, as it may occasionally occur, the adhesion between a flap and its base is not stable enough, and some dead space remains or reestablished itself, the tissue adhesive can be introduced into the cavity at a

Fig. 1. Donor site of the latissimus dorsi flap. Subcutaneous stitches have been placed, the tissue adhesive has been introduced and the hands of the assistant press the two flaps down and together to obliterate any dead space

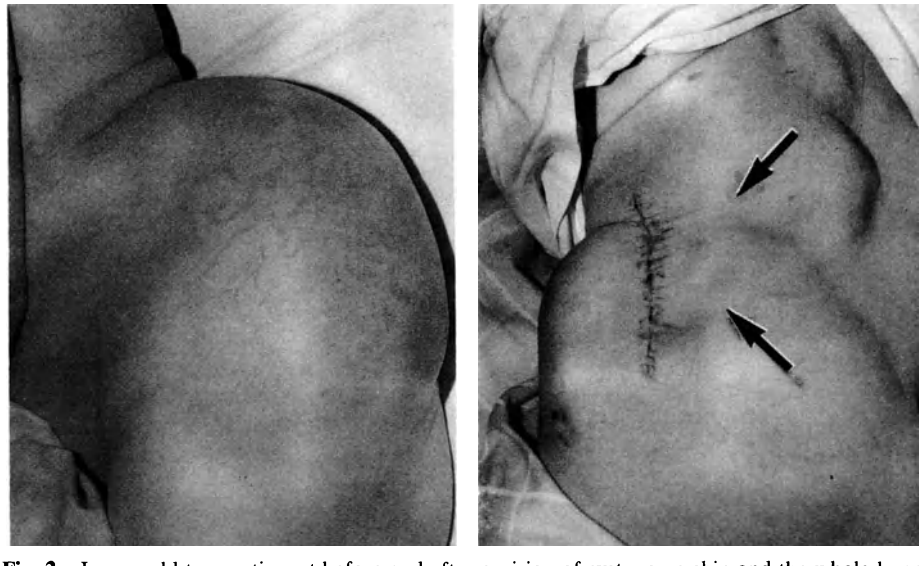

Fig. 2. Large, old traumatic cyst before and after excision of cyst; some skin and the whole large cavity are glued down with tissue adhesive. Note: the deep concave depression (arrows) is only possible because tissue adhesive has been used

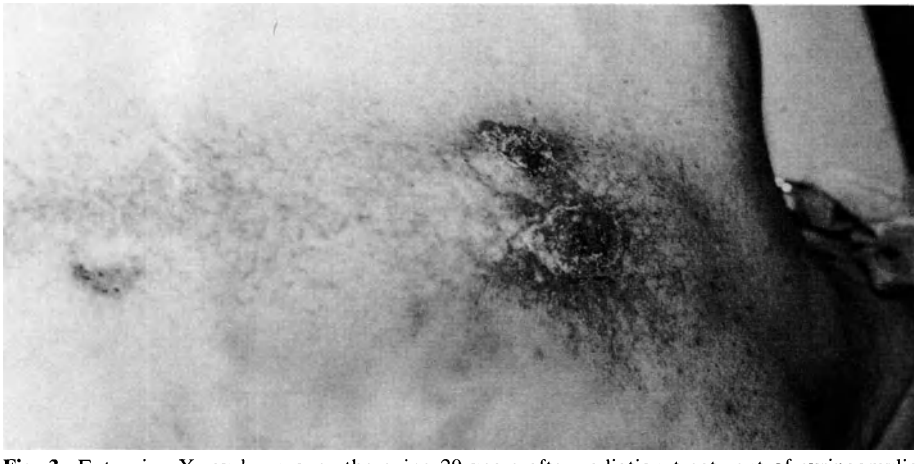

Fig. 3. Extensive X-ray burn over the spine 20 years after radiation treatment of syringomylia. Note: the two exulcerated cancer (squamous cell) areas between the shoulders. A wide excision and two huge sliding flaps were used for treatment

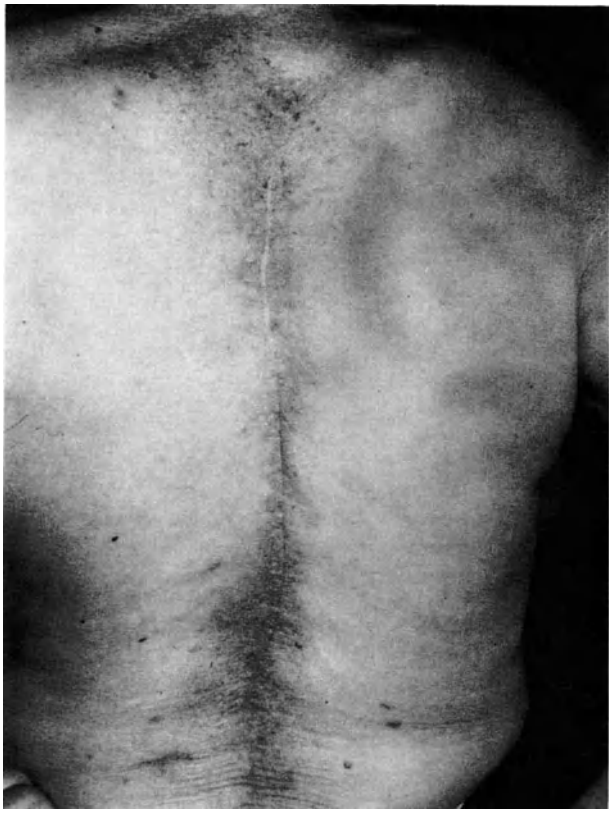

Fig. 4. The same case as in Fig. 3, 4 weeks after the operation. Note the visible relief of the shoulderblades because the skin was firmly glued down to the quite uneven surface of the back

selected later date without anaesthetic and the area gently compressed again for a couple of minutes till complete clotting is obtained. Similar considerations apply to all other cases with foreseeable difficulties in healing, such as in X-ray burns, in syringomyelia and in a combination of both (Figs. 3, 4). (The majority of people with syringomyelia undergo X-ray treatment of the spine at one time or another during their course of treatment in our country.)

5. Treating a great number of various malignancies especially melanomas and scar carcinomas in the lower leg makes radical excision of lymph nodes in the inguinal region imperative. While previously some kind of wound-healing problems, even lymphatic fistulae were quite common, they have become rare after routinely gluing the fairly thin skin flaps together and down over the oval fossa. The dead space is thus effectivly occluded as well. However, the results are not as predictable as in other indications and some complication may still occur, especially if the primary drainage is extensive or some infection is present in the leg area. Repeated fibrin adhesive injection into these secondary fistulae can often resolve the problem.
6. In cosmetic surgery (Bruck), rhytidectomies and abdominoplastics have become the two operations where tissue adhesive is advantageous. While in rhytidectomies with their important but limited areas high concentrations are advisable, in abdominal lipectomies low concentrations should be used. Thus with the same amount of fibrinogen greater quantities of glue are available to spread over the vast wound-area. Since suction assisted lipectomy (SAL) was sometimes performed in the same area with these procedures and the treated regions seemed to profit by it, tissue adhesive might be useful in the rapidly increasing number of SAL cases (personal studies are under way).

Results

The use of tissue adhesive has enhanced primary healing in all the above situations. Statistical evaluation of these – with a few exceptions – is, however, impossible, although more than 600 cases have been involved in this study. The range of variations for the different indications is such that any attempt to analyze the results mathematically must fail. Further units, trying the same approach and communicating their results with each other, might be able to produce statistically significant data.

Discussion

During the past 7 years more than 600 patients have undergone the instillation of fibrin adhesive to their wounds shortly before the end of their operation or later on, when complications occurred. There was not a single complication which could be attributed to the use of this "glue". It has effectively obliterated the dead space which is the cause of many wound-healing problems, e. g. infection, seroma and haematoma. Our experience with tissue adhesive supports the following statement regarding its use:

Advantages

1. There were no proven indigenous complications
2. It is possible to use tissue adhesive in mildly contaminated wounds or after the excision of necrotic tissue (as for instance in decubitus ulcers).
3. Care must be taken that the two components are only mixed in the wound; otherwise the quick clotting will obstruct any syringe and the application will become impossible.
4. Its introduction is completely painless and tissue adhesive can be administered, if need be, without any anaesthetic into wound cavities or fistulae
5. Tissue adhesive reduces complications of residual potential postoperative dead space, e. g. seroma or haematoma.

Disadvantages

1. The effectiveness in dry, clean wounds is predictable and practically standard. In heavily draining wounds, e. g. block dissections or paraplegics, failures and complications are possible. Renewed introduction of tissue adhesive is then indicated to take care of the problem.
2. The preparations are rather expensive, but we feel that the shortened stay in hospital and the fast and uneventful postoperative times for treatment required make its use even financially justifiable.
3. The preparation of the two components takes about 10 min. It should not be shortened or hurried, because insufficient dissolving of the fibrinogen Tissucol even at 37°C may render the whole component less effective. On the other hand prepared components will not remain effective for more than 4 h and they must be mixed at the point of action.

Conclusions

Fibrin tissue adhesive is a valuable addition to the armament of the plastic surgeon in the treatment of wounds with any potential dead space.

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Further Clinical Applications of Human Fibrin Sealant in Plastic Surgery

N. SCUDERI, G. SPOSATO, and G. Di CAPRIO

Key words: Plastic surgery, fibrin sealant, burns patients, hypospadias, rhinophyma

Abstract

Some interesting applications of human fibrin sealant, emphasizing its adhesive, hemostatic and cicatrizing action and the deriving advantages are presented. It is possible to use the human fibrin sealant in skin grafts or mesh grafts either on sites to obtain hemostasis or on recipient sites for immediate adhesion of the graft. In hypospadias correction it can be used to aid the tubulization and anastomosis of the urethra and in rhinophyma operation to obtain an intraoperative hemostasis. A few examples of our clinical experience with fibrin sealant in second- and third-degree burned patients, hypospadias corrections and rhinophymas are reported.

Introduction

In a few years, the use of human fibrin sealant in plastic surgery has become routine. This biological sealant can be used as a substitute for sutures. It controls microvascular bleeding and avoids dead spaces, hematomas and seroma formations.

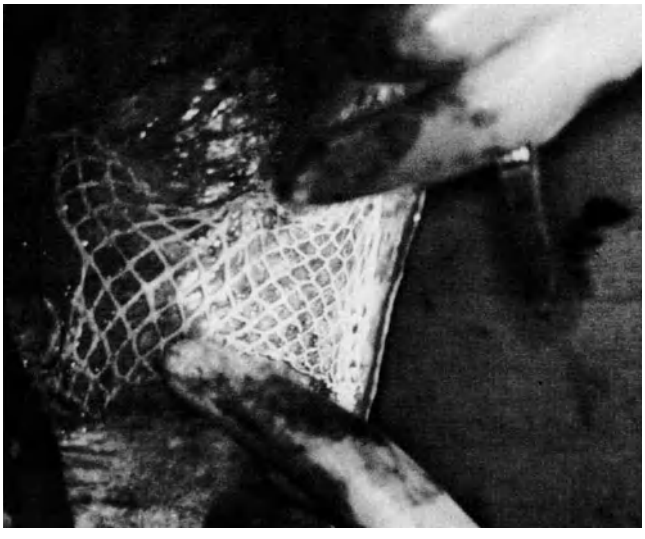

Fig. 1. Mesh graft applied to a burned patient

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Tissucol has several indications, in cosmetic, reconstructive and burns surgery. It is used successfully when fine hemostasis on large bleeding areas is necessary. For example, Tissucol application with the Duploject spray system is used to obtain hemostasis in the donor sites of a split-thickness skin graft producing the immediate formation of fibrin reticulate that produces the hemostasis and formation of a layer of fibrin; it is also essential to permit immediate gluing of the graft on its recipient bed.

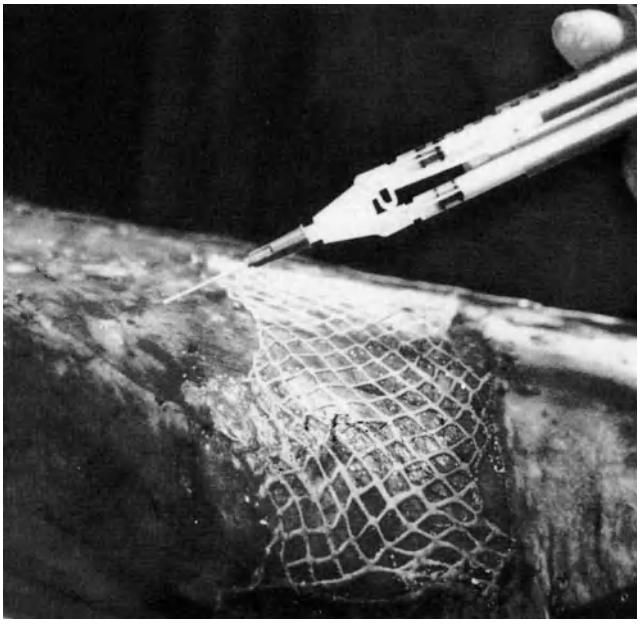

Fig. 2. Tissucol employed for hemostasis and graft adhesion

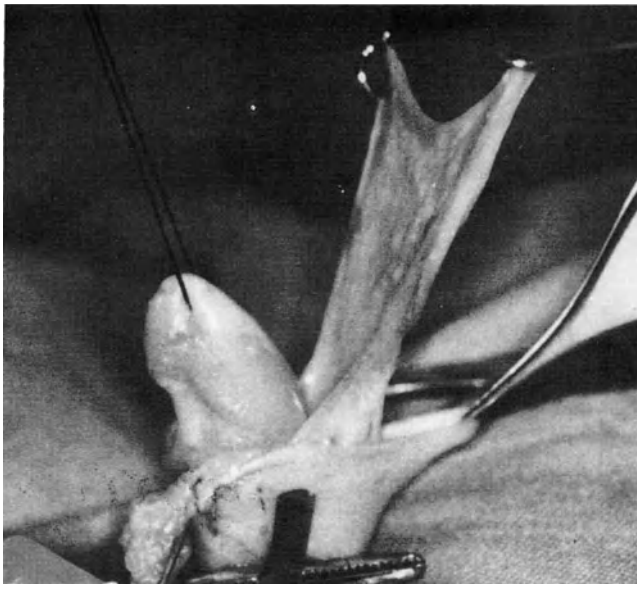

Fig. 3. The preputial pedicle flap and hypospadias correction

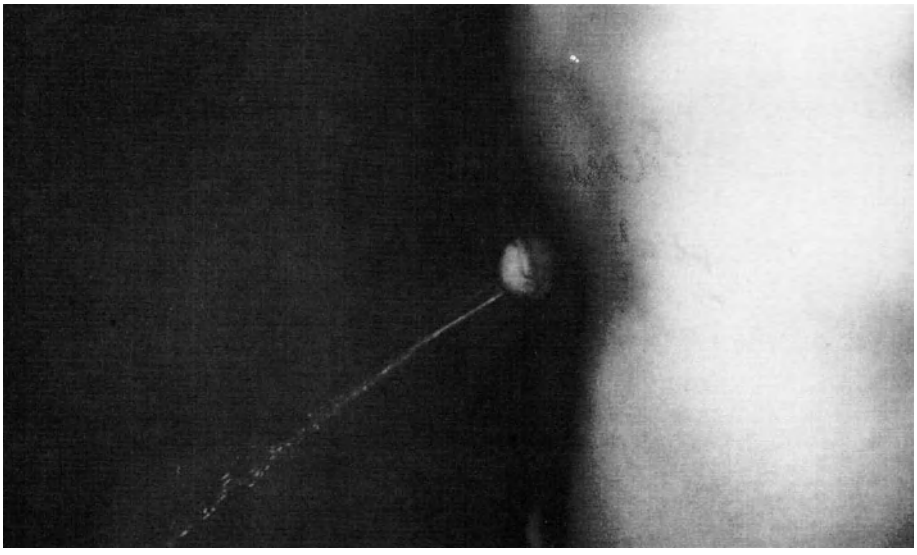

Fig. 4. The result of hypospadias correction

In this way we prevent the hematoma and reduce drastically or eliminate the suture stitches on the borders of the graft.

The sealant can be used every time we have large tissue undermining such as a large flap which can be utilized in reconstructive surgery. This material can be used in cosmetic surgery when we have widespread undermining of tissues in areas where there is hematoma risk, in the face (facelifting), and in cosmetic surgery of the breast mammoplasty and abdomen (abdominoplasty).

We used Tissucol in other plastic surgery applications such as mesh grafts, hypospadias correction and rhinophyma care.

Case reports

Our cases are reported in Table 1.

Discussion and Conclusions

We used Tissucol with the Duploject spray system on the donor site and on the recipient bed of meshed skin grafts in patients who had second- and third-degree burns involving 30% – 70% of the body surface:

Usually the mesh application needs a few suture stitches; this technique can be difficult for different reasons. The sealant needs no sutures, it aids the hemostasis and it stimulates the healing of all the grafted area.

Five patients who had hypospadias were treated with Tissucol. For this correction we used a personal one stage technique that needs subtotal undermining of the

penile skin and of the subcutaneous tissues from the tunica albuginea of the corpora cavernosa. The reconstruction of the deficient urethra was performed utilizing a tubed preputial island flap, which was anastomized with the hypospadiac meatus.

Fibrin sealant is used for the hemostasis and sealing; it reduced complications such as hematomas and fistulae. In these cases we prefer to use needle application and not spray. The fibrin sealant was also applied in rhinophyma surgery (two

Table 1. Cases treated with Tissucol

Patient	Age (years)	Diagnosis	Type of care	Result	Type of Tissucol application
M. A.	2	II° and III° burns with injury of 50% of the body surface	Debridement and mesh skin grafts	Good	Spray with Duplo-ject with 0/2
D. R.	9	II° and III° burns with injury of 35% of the body surface	Debridement and mesh grafts	Good	Spray with Duplo-ject system
S. R.	12	II° and III° burns with injury of 20% of the body surface	Debridement and mesh skin grafts	Good	Spray with Duplo-ject system
G. S.	7	III° burn with injury of 9% of the body surface	Debridement and mesh skin grafts	Good	Spray with Duplo-ject system
D. C.	5	Distal penile hypospadias	Scuderi's technique	Good	Duplojject
T. S.	5	Mediopenile hypospadias	Scuderi's technique	Good	Duplojject
F. F.	6	Glanular hypospadias with recurvatum	Scuderi's technique	Very good	Duplojject
P. T.	4	Mediopenile hypospadias	Scuderi's technique	Good	Duplojject
E. G.	7	Proximal penile hypospadias with recurvatum	Scuderi's technique	Very good	Duplojject
P. P.	63	Rhinophyma	Debridement and spontaneous epithelization	Good	Spray with Duplo-ject system
N. M.	58	Rhinophyma	Debridement and spontaneous epithelization	Good	Spray with Duplo-ject system

cases); we carried out this operation using the technique of debridement with the scalpel. The healthy tissue is obtained with spontaneous epithelization from deep sebaceous glands and from not to involved skin borders. We prefer this method to debridement and skin grafting. Intraoperative hemostasis is obtained with the spray.

It must be emphasized that results have been very satisfactory. The use of fibrin sealant has shown that it is very helpful in various fields and situations related to surgery.

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Fibrin Sealant (Tissucol/Tisseel) and Its Application in Plastic and Reconstructive Surgery

J. HOLLE

Key words: Tissucol haemostasis grafting

Abstract

Indications for the use of Tissucol in plastic and reconstructive surgery can be classified as absolute or relative. For each group different clinical examples are presented and discussed.

Introduction

In 1974 the first application of Fibrin Sealant in humans was performed by the author at the IInd Surgical University Clinic in Vienna, in order to seal an artificial aortic prosthesis. Since that time Tissucol has been used in our clinic in more than 1000 patients with encouraging success and without complications, especially without any reported cases of infective hepatitis [1].

Materials and Methods

Indications for the use of Tissucol in plastic and reconstructive surgery can be divided in to two main groups: absolute and relative.

An absolute indication for the use of Tissucol means that there is no alternative to achieve the same positive surgical results. A relative indication means that the use of Tissucol improves the result or facilitates the surgical procedure.

Absolute Indications

The chief absolute indications for the use of Tissucol are to control diffuse bleeding, especially in cases of haemostatic disorders, to secure surgical correction of liquor fistulas or sutures of the dura, and in the fixation of autologous cartilage and bone grafts in reconstructive cranial procedures.

For each absolute indication I want to present typical clinical cases, starting with the problem of haemostatic disorders. The first case is a 20-year-old female patient who had deep third-degree burns to 45% of the body surface. Following several surgical procedures to remove the burnt tissue, a severe haemolytic disorder was the indication for use of Tissucol to control diffuse bleeding following an escharectomy.

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Simultaneously with the haemostasis, a fixation of skin grafts could be achieved. In another case of a haemophilic A patient, diffuse bleeding occurred from a post-traumatic skin defect on the trunk. Only with the use of the fibrine glue could a skin graft be fixed onto the diffuse bleeding wound.

Large diffuse bleeding wounds can be covered successfully with a fibrin spray to stop the bleeding. Such treatment was indicated in an 85-year-old patient with a third recurrence of a malignant lymphosarcoma in the gluteal region. The tumour was invading the foramen ischiadicum and compressed the ischiadic nerve in this region. In this case palliative resection of the tumour for decompression of the nerve was performed. The whole tumour could not be removed and the resection resulted in a diffuse bleeding tumour surface. In this case the Tissucol spray again was of vital importance in stopping the diffuse bleeding from the tumour surface. No other surgical procedure was as effective as Tissucol in this case.

Now I want to give some clinical examples of the second absolute indication, the sealing of liquor fistulas and dural sutures. The first case is a 58-year-old male patient with an extensive basal cell carcinoma of the cranium, penetrating through the bone into the cerebrum. The tumour could be removed in toto together with the involved parts of the cerebrum. The dural defect was closed with a fascia lata flap and the dural sutures were covered with the fibrinogen glue. The fascia lata flap was covered with a microsurgically transplanted groin flap to close the bone and skin defects. One year after the operation the patient is still alive with no signs of tumour recurrence.

Another very important application for the fibrinogen glue is in craniofacial surgery, since in this area of plastic and reconstructive surgery intraoperative liquor fistulas have to be closed routinely. One such case concerned a 4-year-old girl with a premature synostosis resulting in a dislocation of the left orbita. Using a coronary skin incision the frontal bones were exposed on the involved side, the whole orbita was mobilized subperiostally, and a circularosteotomy of the whole orbita was performed. The whole bony orbita was fixed into the regular position with sutures. One intraoperative lesion of the dura was corrected with nylon sutures and secured by Tissucol. This case is an example of the third absolute indication for use of Tissucol – the fixation of autologous cartilage and bone grafts in the skull. Bone defects around the mobilized orbita were covered with rib grafts, and small contour defects were corrected by fixing grafts into the right position using Tissucol. To demonstrate the use of Tissucol to fix autologous tissue, another case may be presented. A 20-year-old man with a syphilitic hypoplastic nose was operated on to enlarge the soft tissue of the nose with two nasiolabial flaps. After healing of the flaps, cartilage and bone transplantation was performed to reconstruct the bony structures of the nose. All the cartilage and bone grafts were fixed into the new position with Tissucol, and the donor side of the iliac crest was also covered with Tissucol to control the bleeding.

Relative Indications

A relative indication is the use of Tissucol in face lift procedures (especially after intensive undermining in the neck region) to prevent postoperative bleeding. For

this purpose, Tissucol spray gives the best results in preventing postoperative haematomas and oedema and in improving the early postoperative healing period.

Another relative indication is control of diffuse bleeding of the donor site after transposition of thick muscle flaps. In this case the formation of postoperative seromas, especially after transposition of a latissimus flap, can be prevented.

A further important application of Tissucol is in secondary skin grafting procedures. Since we know that skin grafts can be stored at 4°C for about 10 days, they can be used secondarily to cover skin defects during this period. The skin grafts can be fixed onto the wound with the Tissucol spray without using any sutures and thus without any discomfort for the patient.

In our opinion the application of Tissucol in peripheral nerve surgery is only indicated if the nerve has to be implanted into the muscle for neurotization of the muscle. The nerve can be fixed after implantation with Tissucol at the surface of the muscle. We do not think that Tissucol is of great importance in peripheral nerve suturing or transplanting procedures, except in selected cases. The advantages of Tissucol compared with simple nerve sutures are still under discussion.

Discussion

A disadvantage of Tissucol in the field of plastic surgery is that Tissucol with a higher apronitin concentration results in retardation of fibrinolysis, with the effect of disturbing normal reparative tissue processes. This can be a problem in peripheral nerve anastomoses or in skin grafting procedures. On the other hand the advantages of Tissucol in plastic surgical procedures are of great importance and we have been able to demonstrate that its application in the right cases is highly effective and cannot be replaced by other methods. There are nearly no negative complications with this technique and its use is quite simple.

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Specific Indications for Fibrin Glue in Plastic and Craniomaxillofacial Surgery

M. STRICKER, Ph. MAXANT, and A. CZORNY

Key words: Fibrin sealant, plastic surgery, craniomaxillofacial surgery, réunion immédiate

Abstract

The fibrin adhesion system has proved highly efficient in many fields of surgery. The fibrin sealant Tissucol is especially indicated in the fields of plastic and craniofacial surgery in accordance with two aims: technical and biological.

Technical Viewpoint

The fibrin adhesion system has four advantages: it is simple, safe, stable and fast. It provides an improvement in all cases, coping with difficulties of suture, maintenance, and prevention of wearing the dressing: skin grafting, nerve grafting, mucosal sutures on the hard palate in the retroalveolar area, dural sutures, and repair of the skull basis and ear.

Biological Viewpoint

It could be of great interest in the future to increase local blood supply in flaps and scars, with less risk of infections and necrosis.

Joindre le separe, a very old aim of the surgical art, was the struggle between partisans and opponents of the primary suture. Once primary sutures were admitted in principle, many variations of suture type and material appeared. A historical survey leads us to discern three periods in the evolution of ideas:

1. The first (Hippocrates) was the development of a dogma based on the natural processes.
2. The second was the English period of clinical application, especially to treat amputation.
3. The last was the French period of extension through the different fields of general surgery.

An analytical study of the primary suture shows the predominance of local factors, primarily the precise adhesion between the wound edges. Every separated living tissue tends towards adhesion, as noted by Cruveilhier, with his law of restoration by way of the blood supply, according to Hunter.

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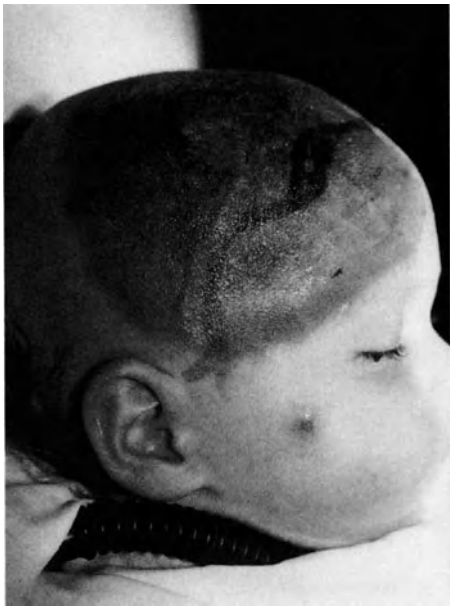
Because the adhesion system is a natural process, closing the wound edges is a logical treatment; nevertheless, the choice among a lot of materials was not easy. Collodion, cyanoacrylate, resins, and adhesive bandages were unsatisfactory attempts in most cases because of toxicity.

The use of fibrin sealant to clot tissues is the logical result of experiments. Hunter, Maunoir, and the Montpellier school differentiated primary adhesion purely by



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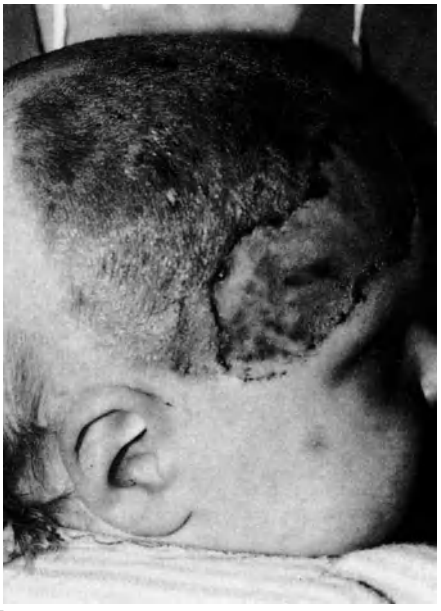

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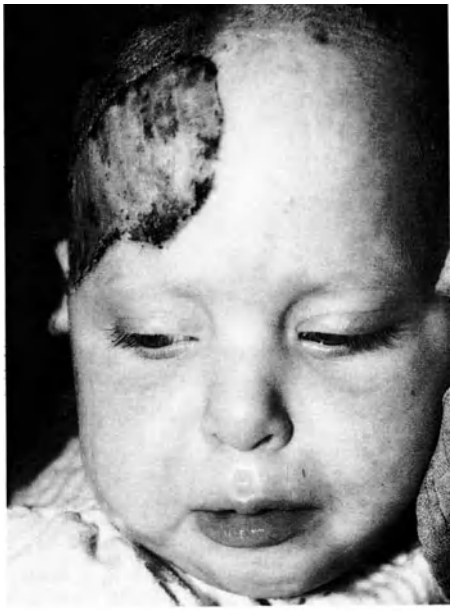
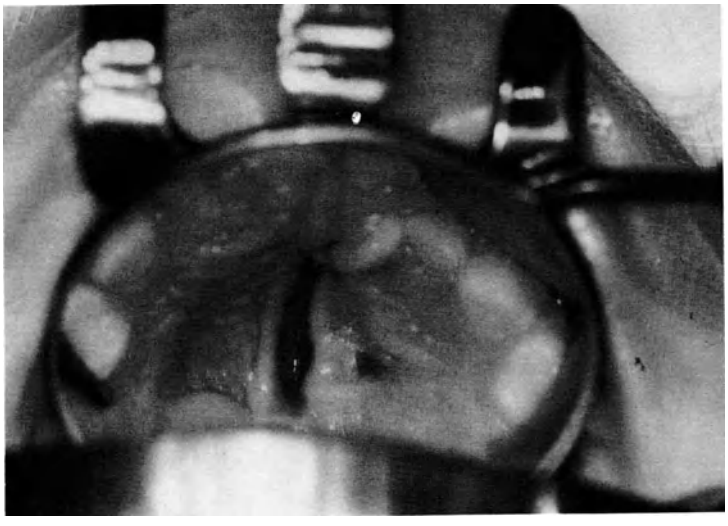


c

Fig. 1a–c. **a** Craniofrontal naevus in a child; **b** resection of the frontal part; **c** repair by a split-thickness graft from the scalp on the controlateral side. The graft is clotted by Tissucol

bleeding from secondary adhesion by inflammatory process, and fibrin sealant is just a direct consequence of bleeding adhesives.

The fibrin sealant (Tissucol) has proved to have a high degree of efficiency in the surgery of soft tissues and in bone surgery, in accordance with technical and biological aims. Use of this material is simple, safe, stable, and fast, and it could in the future improve blood supply in flaps and wound healing. Fibrin sealant has become a standard method for joining separated tissues: for stabilizing small pieces of bone or soft tissues with a high level of accuracy, for facilitating handling as well as improving wound healing, directly by vascular stimulation and indirectly by uneventful healing. Whether it is exclusive or complementary, this glue is used for a number of different indications.



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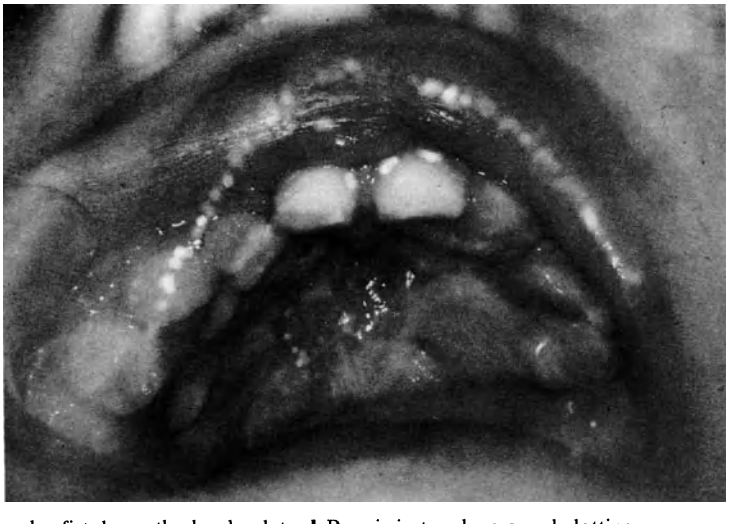
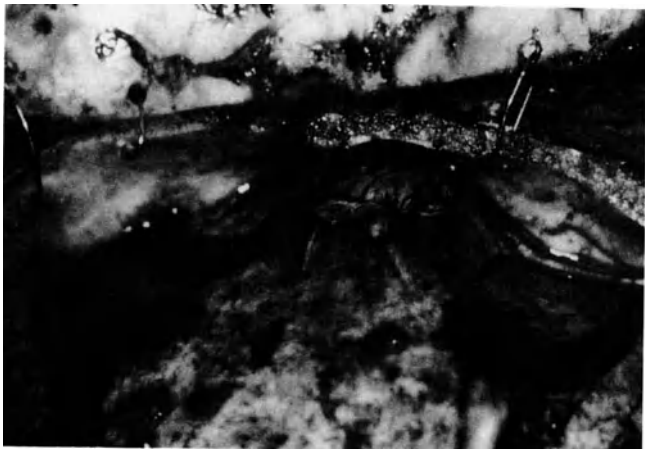


b

Fig. 2a, b. a Retroalveolar fistula on the hard palate. **b** Repair in two layers and clotting

a



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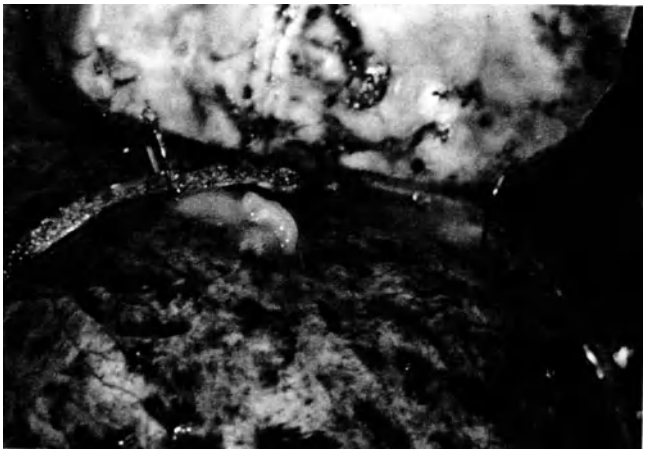

c

Fig. 3a–c. Defect of the bone and dura mater on the anterior part of the basicranium. Closure by a chip of bone and grafting a piece of pericranium, secured by fibrin sealant

Preferential Indications

To Prevent Mobility. Split- or full-thickness skin grafts can be firmly secured, as a result of the glue's hemostatic and adhesive properties, on the circumference and on the undersurface. Advantages are no displacement of the graft, reduced operating time, greater benefit for children.

To Reduce Surgical Trauma. Clotting is useful in the case of dermabrasion, or when small pieces of skin or soft tissues have to be arranged. In bone surgery, minor comminuted fragments, once adapted, are secured in place with the glue.

To Join Areas Difficult to Reach. A standard suture is not easy in areas full of deep crevices. Fibrin sealant can be used at the retroalveolar part of the hard palate to close fistulas and at the cranial base to repair dural defects with an epicranial graft.

Complementary Indications

Along with a standard suture with stitches, fibrin sealant is used to reinforce healing in a secured position.

Neural Sutures of Anastomoses

The first clinical attempt in humans was during a nerve grafting procedure (Matras). An interfascicular arrangement can be achieved without tension and with minimal risk of fibrous reaction. Nevertheless, experiments by Magalon and coauthors lead us to think that glue blocks axonal progression.

Conclusion

Fibrin sealant is a physiological and useful tool, taking its place among the daily standard techniques to suture with minimal inflammatory reaction, harmless and without increase of the infection rate. It promotes wound healing and serves as a tissue adhesive.

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Fibrin Sealant in Burn Injuries – Experimental Study

G. BLÜMEL, R. ASCHERL, S. HAAS, K. GEIßDÖRFER, A. STEMBERGER, G. SCHÄFER, W. ERHARDT, and O. PETROWICZ

Key words: Fibrin sealant, burn injuries, skin grafts

Abstract

Fibrin sealant was investigated in experimentally induced local burn wounds. Application of fibrin sealant onto postexcision wounds by a spray apparatus yielded both good epithelialization and wound closure. In combination with various skin grafts (mesh graft, split thickness graft, and free flaps) the fibrin sealant reduced the risk of graft failure.

The clinical significance of burn injuries is highlighted by the following figures: 300 000 of the 2 000 000 people who sustain burn injuries per year in the USA require hospitalization.

Due to the size and degree of their burn injury 20 000 individuals are referred to centers specializing in burn treatment, and 12 000 patients die as a direct result of their burn injury [6].

When a burn wound exceeds 40% of the body surface area, mortality increases disproportionately. Children and elderly patients are affected most severely.

Local Treatment of Burn Wounds Using Biological Materials

The local application of biological materials in severely burned patients is an old therapeutic measure since cadaver skin and porcine skin were used in the last century.

The first reports on local wound covering by fibrinogen and thrombin were published by Cronkite et al. [3,4].

Recent papers by Gallico et al. [5] and Burke et al. [2] reveal the success of utilizing cultured epidermal cells on severely burned patients.

Experimental Model and Methods

For testing various burn wound coverings the following experimental model was used.

A metal stamp is heated (170°C) and placed on the dorsolumbal region of anaesthesized rats under mild manual pressure for 30 s, inducing a third degree burn injury. The size of this thermal injury can be demonstrated by intravital staining as

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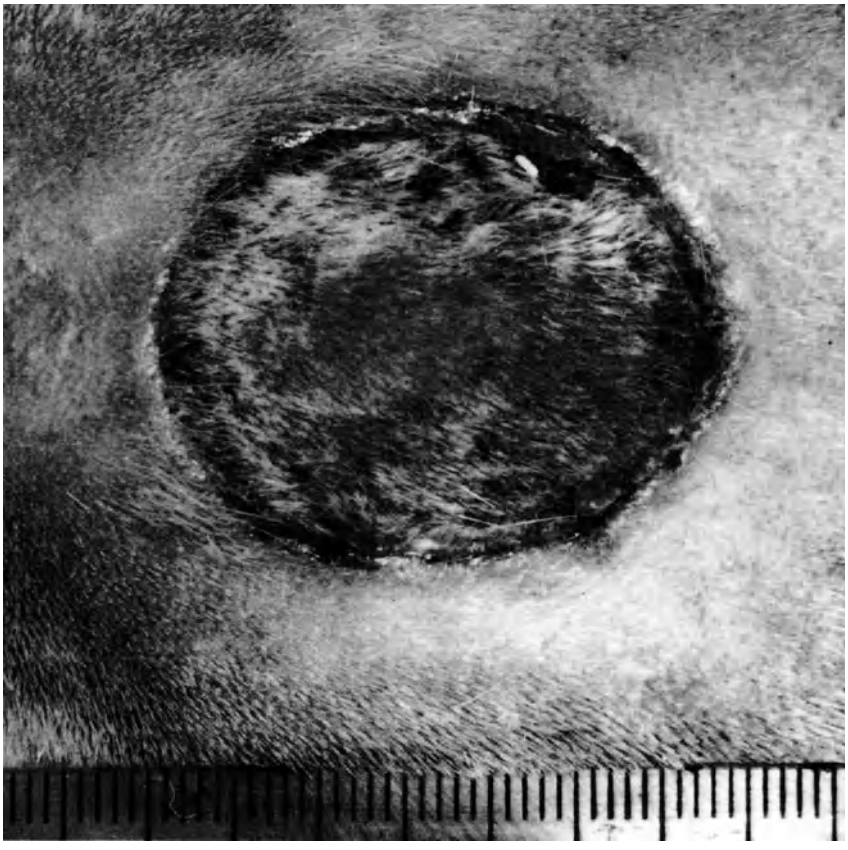

Fig. 1. Intravital staining of an experimental burn wound in the dorsolumbal region in an anaesthetized rat

shown in Fig. 1. The day following the injury an excision to the fascia is made and the agent or material to be tested applied.

The following measures have been studied:

a) fibrin sealant
b) various skin transplants (mesh graft, split thickness skin, skin flaps)
c) temporary biological wound dressings on the basis of collagen,
d) cryopreserved skin.

For estimation of the therapeutic effects in our experiments the following parameters were used:

a) macroscopic aspect
b) planimetry,
c) microangiography,
d) histology,
e) thermography.

The observation period was usually 12–14 days.

The Local Application of the Fibrin Sealant

In the first series the burn wound was sprayed with fibrin sealant following excision using a device designed and developed at our institute.

All together there were eight groups according to the various concentrations of thrombin and aprotinin.

Excision wounds following burn injuries as well as excision wounds without any burn trauma served as controls.

The macroscopic aspects revealed a superiority of the treated burns as compared to the burn controls. There was no bulging of the wound edges with the more rapid epithelialization (Fig. 2). Histologically there was better reepithelialization, particularly under the fibrin layer, with a more homogeneous granulating tissue underneath. In the controls the invading epithelium was accompanied by irregular and cell rich granulating tissue. Micromorphometric studies confirm both the macroscopic and microscopic findings. In the treated wounds the content of collagen fibers and the thickness of the granulating tissue are superior to the controls. The remaining wound surface at the end of the experiment (12 days) is significantly less in the treated groups (Fig. 3). Best results are found in the groups with high levels of aprotinin.

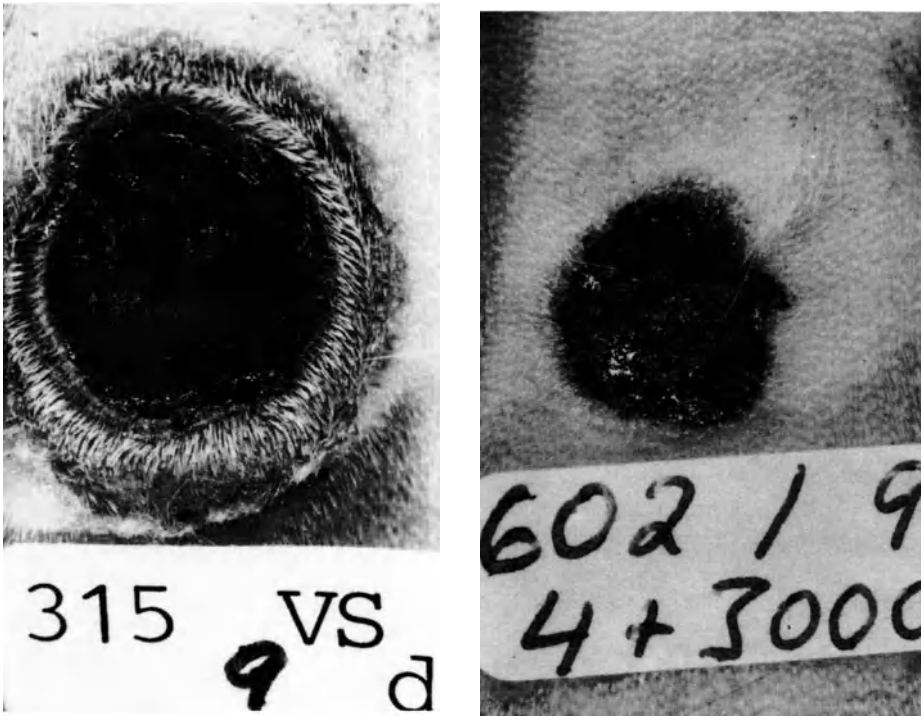

Fig. 2. Fibrin-treated postexcision burn wound (*right*) with a high concentration of aprotinin (3000 KIE). Burn wound, control (*left*). Note the bulging of the wound edges

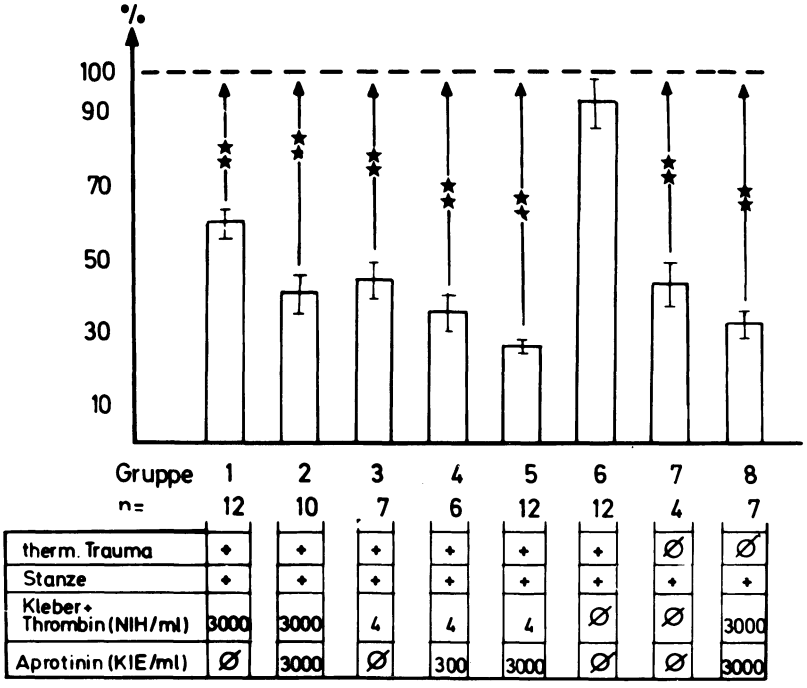

Fig. 3. Comparison of fibrin-treated postexcision burn wounds (*groups 1–5*) with postexcision wound controls (*group 6*), postexcision wounds (*group 7*) and fibrin-treated postexcision wounds (*group 8*). 9 days postoperatively, 100% = postexcision wound area

Fibrin Sealant and Skin Grafts

Syngeneic skin transplants (mesh graft, split thickness skin, free flaps) were performed with the additional use of fibrin sealant. In this experimental series the same model was employed as described above.

When free flaps were transplanted, little drops of the thrombin component and fibrinogen were placed on the underside of the transplant. Using mesh graft the fibrin sealant was applied both on the graft and implantation sides. When split thickness skin was used, the underside was moistened with the fibrin sealant.

All the transplants were covered by nonadherent gauze dressings with a cotton wedding stent on top. Excess fibrin adhesive must be removed in order to prevent an interface developing between the graft and the wound. This can be achieved by "rolling" the graft, yielding an intimate contact with the underlying tissue.

In the split thickness graft the additional use of fibrin sealant produced better results. The acceptance of the graft was superior and revascularization more rapid. As a parameter of the healing of the grafts, thermographic evaluations demonstrated a significantly better healing when fibrin sealant was applied. Planimetry of isothermic areas revealed a statistically significant superiority of the fibrin sealant treated transplants (Fig. 4).

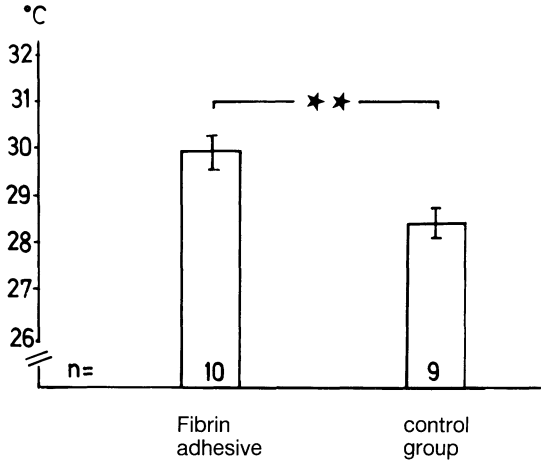

Fig. 4. Thermographic evaluation of split thickness skin grafts

Healing of the free skin flaps also appeared to be improved when fibrin was used. The initial fixation as well as the primary blood clotting in the wound led to healing of all the flaps transplanted. Even the gaps inbetween the flaps were reepithelialized more rapidly.

The histological investigation demonstrated both the good epithelialization and the vital healing of the transplant (Fig. 5).

In the mesh graft groups epithelialization in the meshes was enhanced also by the fibrin sealant. As far as experimental results can predict clinical usefulness, fibrin seems to be of particular value in mesh grafts. Our experimental findings confirm clinical results [1] as well as the report by Spängler et al. [7], which has to be considered a "classic".

Teh [8] applied fibrinogen and thrombin in burn wound treatment but did not find this useful. He also studied local treatment with aprotinin especially under the aspect of inhibition of bacterial fibrinolysis. But this author did not study a true fibrin adhesive system utilizing aprotinin to stabilize the applied fibrin which he expected to be one of the most important factors of skin graft healing in potentially infected wounds.

Further Prospects

With extensive burn wounds a sufficient amount of autologous skin transplant can not always be harvested. Sometimes problems also occur in the donor sites.

A collagen film from bovine type I-collagen has been developed which can be glued onto the excised burn wounds using fibrin sealant. Furthermore this film also can serve as a dressing for skin grafts.

The particular advantage of fibrin sealant in burn wounds consists in an enhancement of healing; the fibrin sealant serves as a scaffold for both granulating tissue and epithelium. The significance of fibrin sealant in cases of skin transplantation lies in assisting blood to clot in the wound and the fixation of the graft and in an enhanced revascularization.

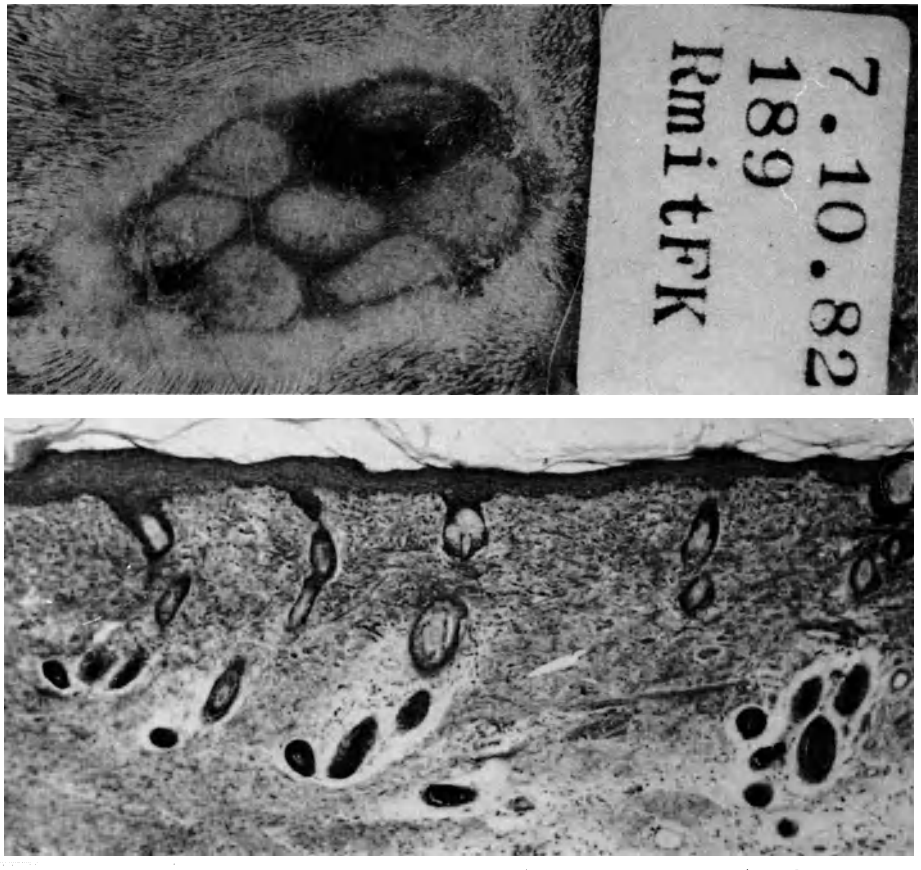

Fig. 5. Wounds healed by free flaps with fibrin sealant (14 days postoperatively). *Below* shows the complete reepithelialization of the burn wound with vital healing of the transplant on the postexcision burn wound (Elastica Ladewig) 19×

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Skin Grafting with Fibrin Sealant in Burns

R. HETTICH

Key words: Burns, fibrin sealant, split skin grafts, mesh grafts, mixed skin grafts

Abstract

The author presents 6 typical cases of plastic surgery to demonstrate the management of minor and major burns with fibrin sealant. Using the Duploject Application System, extensive mesh grafts as well Chinese mixed grafts are successfully anchored in the recipient beds. The same technique is applied to treat large donor areas of split thickness skin grafts; one of these was additionally covered with transparent polyurethane foil.

In minor burns just the fibrinogen component of the sealant is applied to the graft and thinly spread with a finger, while the thrombin solution is applied to the recipient bed. Activation of the fibrin sealant is brought about when the graft is applied to the recipient area. In this way, excessively thick fibrin layers and their negative effects on wound healing are avoided.

Introduction

For various reasons, the surgical closure of extensive burns often is a considerable problem. Apart from the fact that the donor area available for the removal of autologous skin is insufficient in many cases, the hemorrhage caused by the tangential excision of skin grafts constitutes the crucial factor limiting the extent of such procedures.

Both laser technology and electrocoagulation have been found to be inadequate in the prevention of these hemorrhages, which may lead to 2 serious problems. Blood loss often may become excessive, although this is hard to assess, and the graft take may be jeopardized by the accumulation of blood between the graft and the recipient bed.

The local application of ornipressin and compresses of hot saline can reduce the bleeding and, as a consequently, the number of necroses caused by the use of electrocoagulation for hemostatic purposes decreases considerably. These necroses also have a negative effect in transplantation. Aside from infection, hemorrhage is the most frequent cause for the failure of transplantation. This applies especially to Thiersch's grafts, which cannot be replaced by mesh grafts in the region of the face and the hands. Only the use of mesh grafts prevents hematomas with some certainty.

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This situation has fundamentally improved since fibrin sealant has become available. Its use considerably diminishes the risk of bleeding beneath the graft and at the same time ensures intimate contact between the graft and the recipient site, leading to higher rates of graft incorporation, in particular with skin grafts other than mesh grafts.

But even in the case of the rather unproblematic mesh grafts, fibrin sealant has a series of advantages due to better graft fixation and, inter alia, reduction in operation time.

Material and Methods

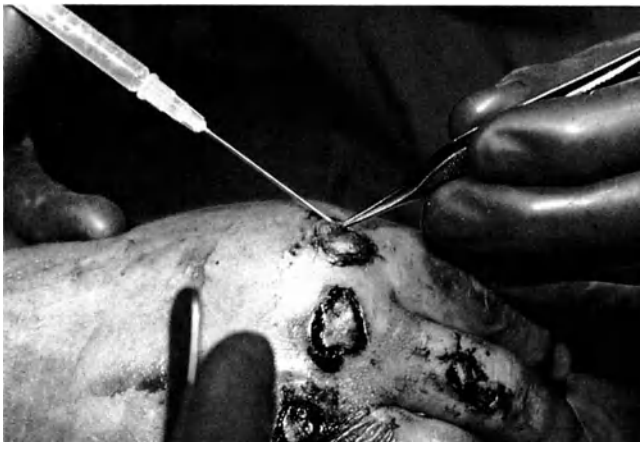
In the cases presented below, the fibrin sealant was applied by 2 different methods.

In the repair of major skin defects, e.g., in skin grafting for burns, we prefer spray application using the Duploject system. At a pressure of about 2 atm the fibrin sealant solution and the thrombin solution are ejected from two separate jets and blend as they are sprayed in two overlapping cones across the surface to be sealed. By spraying at a distance of approximately 15 cm, the two components are evenly distributed across a circular area and result in a delicate fibrin film. When the low thrombin concentration (vials a + b) is used, there is sufficient time after spraying for spreading any collections of activated but still liquid fibrin sealant, using a clean surgical glove, to avoid the formation of thick layers of fibrin between the graft and the recipient bed. After manual removal of surplus fibrin, the entire area is covered with the grafts which are approximated by subtle pressure. The low thrombin concentration used allows sufficient time for graft approximation. While the fibrin film is setting, no polyvinylpyrrolidone-iodine preparations should be used, as this would prevent the conversion of fibrinogen into fibrin.

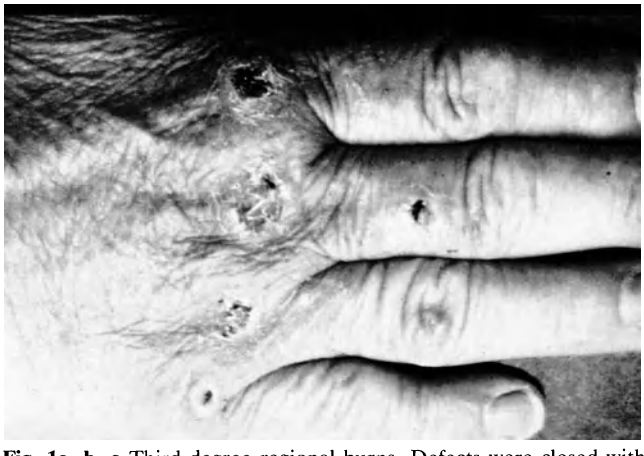
In the case of minor skin graftings, the fibrinogen component is applied to the transplant and an equal quantity of the thrombin solution to the recipient bed and spread by the operating surgeon with his finger or hand. In these cases the high thrombin concentration (vials a + d) is always used, which leads to rapid solidification of the fibrin sealant when the 2 surfaces are joined. Nevertheless, 1–2 min are left for approximation of the graft.

Case Histories

One of our patients had burnt herself on a laundry mangle. After primary excision of the third degree regional burns on the extensor surface over the metacarpophalangeal joints of the index, middle, and ring fingers, the defects were immediately closed with thick-split grafts which were fixed with the fibrin sealant without any sutures. After mobilization of the patient on the sixth postoperative day (Figs. 1a, b) primary healing occurred with optimum functional and aesthetic restoration. The donor area was sealed with the rest of the fibrin sealant. No additional dressing was required. The absence of pain throughout the postoperative course was favorably noted by all patients. In the case of donor areas that are larger in size, but can still be treated on an out-patient basis, it is recommended that the



a



b

Fig. 1a, b. a Third degree regional burns. Defects were closed with thick-split grafts which were fixed with the fibrin sealant. **b** Primary healing on the sixth postoperative day

film of fibrin sealant be protected with highly transparent polyurethane foil so that clothes can immediately be worn over the wound area. The wound area remains clearly visible only when bleeding into the space between foil and wound is prevented by fibrin sealing. Especially with donor areas on the head, the additional application of polyurethane foil has been found practical, as pains due to the position in bed are avoided, as is sticking of the bedclothes to the wound area (Fig. 2). The highly painful change of wound dressings that often causes bleeding, as in the typical case of a donor area on the thigh, are completely avoided by this type of management.

Especially in elderly people, in this case a 74-year-old patient with a third degree burn, the fixation of grafts by dressings is a particular problem, especially in the thoracic area where it may impede the breathing excursion. In this particular patient the entire defect left after primary necrectomy was covered with mesh grafts which

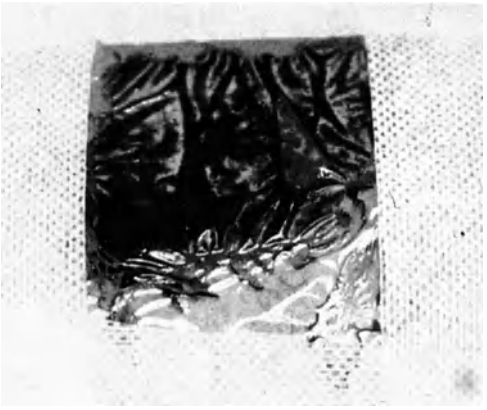


Fig. 2. Application of polyurethane foil

were exclusively fixed with the fibrin sealant. The donor area on the thigh was likewise coated with the sealant, so that the patient could be instantly mobilized and was able to leave his bed for physical therapy since he was largely free of pain.

The patients, shown in Fig. 3a was in an extremely poor state of health, when admitted to our departement. His extensive burns had been treated in Afganistan and Pakistan for 2 ½ years without healing either the burns or the donor areas. The Chinese technique of mixed grafting was followed, which is also facilitated by fibrin adhesion. The patient was treated for 2 weeks to improve his general condition before we began to transplant perforated skin from dead bodies to the granulation defects (Fig. 3b). After 2 days autologous skin was implanted into the perforations in all places where the homografts had taken and the entire area of the mixed grafting was coated with fibrin sealant and a collagen film. The latter was removed only 3 weeks later. By that time the donor area on the pilous skull had also largely

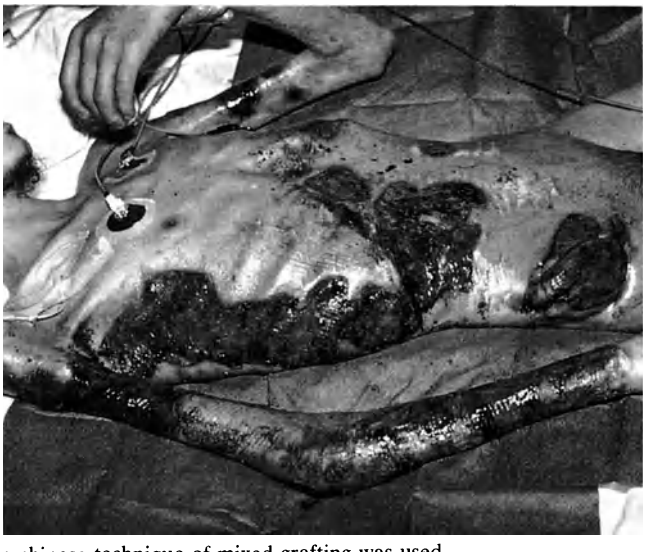


Fig. 3a

Fig. 3. In this burn patient the chinese technique of mixed grafting was used

Fig. 3b

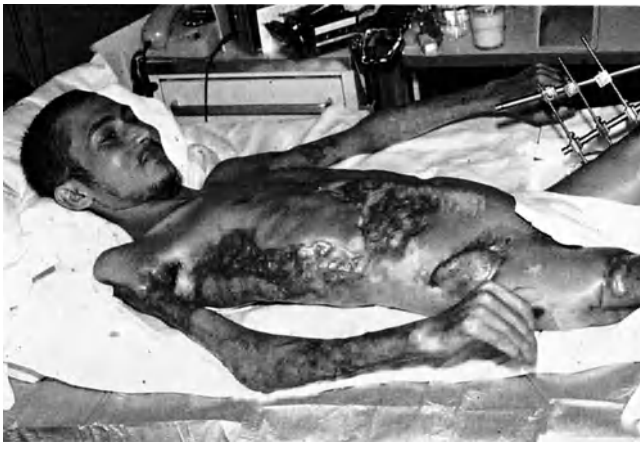


Fig. 3c

healed so that after taking split-thickness skin grafts on the head three times we obtained successful repair of all defects by the use of these mixed grafts. In all these cases autologous skin was removed to cover at most 10% of the wound area. Figure 3c shows the patient 8 weeks after admission to our hospital.

Even in the management of facial burns, fibrin sealing marks an important step forward as fixation of grafts by conventional techniques is very difficult. In the last case treatment of third degree facial burns showed a satisfactory primary result after primary excisions and covering by fibrin sealant without sutures or fixation with bandages.

Discussion

The various techniques of skin grafting with fibrin sealant briefly high-lighted in this presentation give just a few examples of the spectrum of uses of this new technique of physiological tissue sealing. The advantages for the surgeon are obvious: Shortening of the operation time without suturing, allowing precise wound edge approxima-

tion and fewer dressings, which is a relief for the patient; no more crusty adhesion of bandages causing pain when removed. If fibrin sealant is used in plastic surgery, the operated surface is dry and without pain; the same happens with the donor area of the split thickness skin graft that is known to cause considerable pain.

The influence of fibrin sealing on wound healing cannot be defined after these case reports. Based on clinical experience, however, we found no indication of delayed or impaired healing of the grafts or the donor area of the split thickness skin grafts.

Fibrin Sealing in the Treatment of Burn Wounds

A. GRABOSCH

Key words: Fibrin sealant, burn wound, split-thickness skin grafting

Abstract

The problems of split-thickness skin grafting on burn wounds are discussed. By use of a two-component fibrin sealant we tried to get better results in grafting. The fibrin sealant is described exactly as well as the technique used to seal the split skin grafts. Indications for sealing grafts on burn wounds are given. To get more objective criteria we made histological examinations of small excisions of grafted skin sealed and nonsealed. Initial results are reported. The clinical experience and the histological findings show the advantage of sealing split-thickness skin grafts on burn wounds.

Introduction

Patients suffering from extensive thermal damage of the body surface are first of all endangered by hypovolemia – caused by the loss of plasma into the extravascular space. If the patient is able to overcome this acute dangerous phase, further danger of life occurs by infection through the extensive wounds. This may lead to septicemia and possibly to death. In spite of isolation and the use of topic agents only the definite closure of the wounds as quickly as possible can secure protection against bacterial infection. Operative therapy therefore is the most important point in the treatment of severely burned patients. This means removal of necrotic skin areas and skin-grafting – by mesh grafts to cover a large surface. It is a great problem that there is only a very small donor area for taking autoplastic grafts in the case of extensive burns. To solve this quantitative problem, as many grafts as possible must be taken. The correct choice of the time of grafting – when a well-vascularized exuberent granulation or a clean wound-area without necrosis can be seen – and the correct technique of grafting are most important.

Nevertheless again and again part of all the grafts are not accepted. One has to visualize that the grafts only laid on the wound or fixed with some stitches have to be supported by diffusion from the wound ground. Examinations into this problem were, for example, published by Converse [2] in 1969. About 3 days later vascularization starts. This vasculogenesis is decisive for further healing. Especially within these first days this tender vascularization can be disturbed. First of all mechanical factors have to be mentioned here. A strong exsudation, typical of infected wounds,

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or hematoma following insufficient hemostasias' establish another barrier between graft and ground. Dressings put on the grafts or touching the grafts with wet compresses cause tangential forces which may destroy the sticking of the grafts or tear off the soft vessels. So the destiny of the grafts is sealed. With the background of all these ideas we tried to get better results in skin-grafting by using a fibrin-sealing system to fix the grafts.

As early as 1944 Cronkite and coworkers [3] as well as Tidrick and coworkers [13] tried to fix skin grafts by the use of fibrinogen and thrombin. As only a very weak effect could be achieved, this method did not come into general use initially. Further important steps on the way to tissue-sealing as it is applied today were the discovery of fibrin-stabilizing factor, factor XIII, by Laki and Lorand [5] in 1948, its detailed characterization by Loewy and coworkers [6] in 1961, the use of fibrinogen cryoprecipitate by Matras [7] in 1972, and detailed experimental studies by Matras [8] in 1970, by Spängler and coworkers [11] in 1973, and by Braun and coworkers [1] in 1975. In 1973 the first clinical use took place. In 1977 Staindl [12] was the first to publish experiences and results in 28 cases of sealing skin-grafts after excisions of tumors in the face and neck.

Further publications, dealing with sealing skin-grafts, followed. But all these fixations were made in noninfected areas.

In 1979 Frey and coworkers [4] published their experiences in delayed skin-grafting, and in 1980 Rendl and coworkers [9] gave a report of skin-grafting in cases with ulcus cruris. We have been using a two-component fibrin-sealing system since 1984 to cover the presumably most problematical skin defect – the extensive burn-wound. Very often these patients fail to meet the claim for accepting the grafts: for the following reasons:

1. The area that has to be grafted shows necrosis and, caused by this, poor chances of vascularization.
2. Very often we have a coagulopathy and a hematoma underneath the graft because of this.
3. Nearly all the wounds are infected.
4. Because of the necessary intensive therapy of the severely burned patient it is nearly impossible to immobilize the grafted areas.

Material and Method

The fibrin-sealing system we used, Tissucol (Immuno, Vienna), consists of two components. The first component contains the human fibrinogen-cryoprecipitate at a concentration of 90 mg/ml as well as factor XIII (10–50 units), fibronectin and plasminogen. The second component contains an aprotinin-calcium chloride-thrombin solution with an aprotinin concentration of 3000 IU and a thrombin concentration of 4 IU/ml.

We use this high concentration of aprotinin because of the high fibrinolytic activity of the infected area that has to be grafted. The low concentration of thrombin is used to get a complete mixture of both components before coagulation can take place. This is very important, as Seelich and Redl [10] demonstrated. With this mixture homogeneous clots of maximal solidity are formed. Between October

1984 and March 1985 we sealed about 30 grafts in 20 patients. All patients suffered from deep second-degree or third-degree burns or scalds. Examinations of the areas we intended to graft showed contamination by *Staphylococcus aureus, Streptococcus faecalis, Pseudomonas aeruginosa, Candida albicans* and others.

Most of our patients showed disturbances of the prothrombin complex evoked by burn disease. We carried out necrectomia after systemic stabilization and exact demarcation of the burned area.

As a rule we fixed the grafts during the same operation or a few hours postoperatively in the intensive care unit. In a few of our cases we first covered the wound ground with cadaver or pigskin for some time and did the grafting 2 or 3 days later, when the ground showed a good chance of accepting the grafts. We sealed mesh-grafts as well as sheets.

To achieve a good result a special standardized technique is needed. We try to create a ground for the graft that is as fine as possible by tangential or deep excision of the necrosis and very careful macroscopic blood-staunching by electrocoagulation and putting on some wet, warm compress, which we prepare with Ornipressin.

After that we dab the ground once again. It is very important to take away all the bigger coagula. Then we put the grafts – which we laid on tulle grass previously – in their proper places. The assistant raises the grafts again while the operator applies the fibrin-sealing system (Figs. 1–3).

We think that it is very important to lay a very thin and homogeneous film of fibrin in order not to produce a further diffusion barrier under the graft. For that purpose spraying both components with filtered compressed air from a distance of 10 cm is very suitable. We do this by the help of the Tissomat. Once again we put the

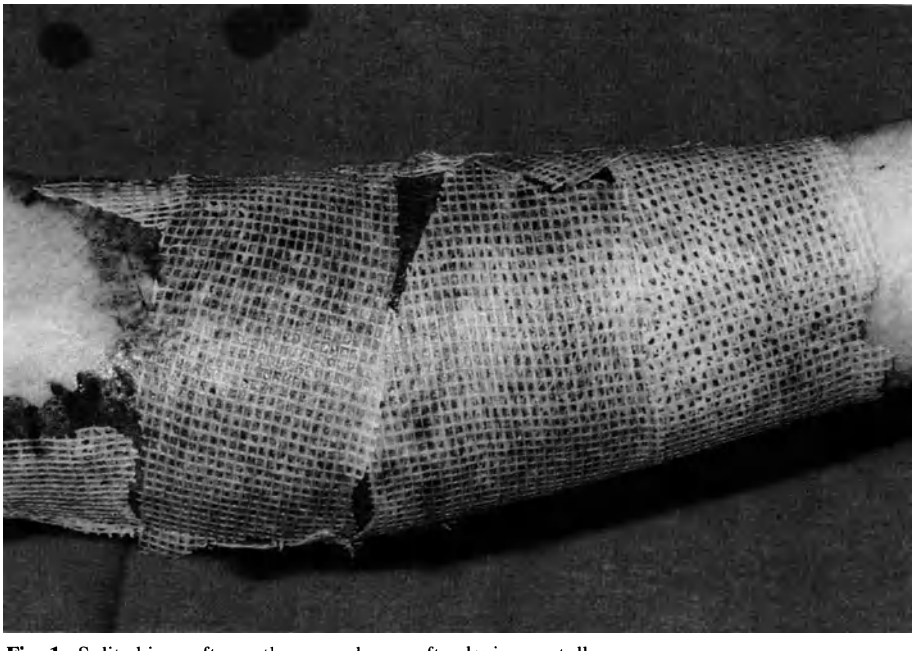

Fig. 1. Split-skin grafts on the wound area after laying on tulle gaze

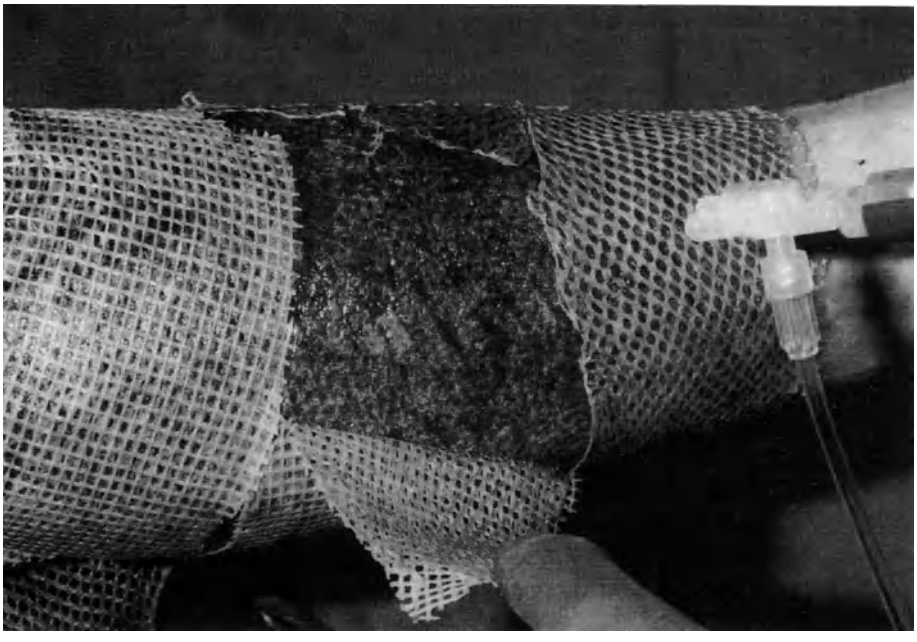

Fig. 2. Application of fibrin sealant by the spray technique

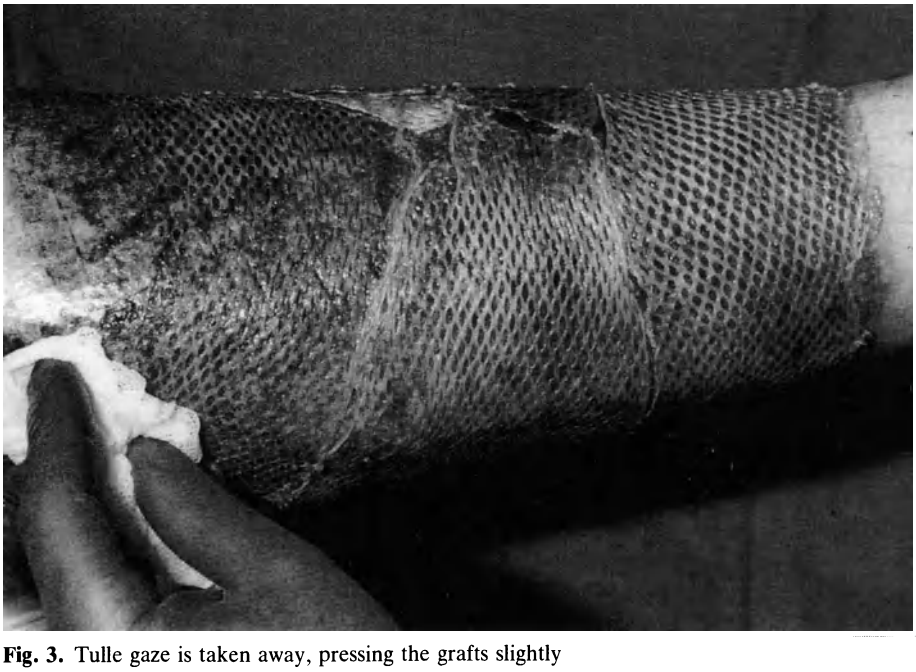

Fig. 3. Tulle gaze is taken away, pressing the grafts slightly

grafts on the ground. We take away the tulle grass and press the grafts carefully. Further treatment is open. For 72 h we keep the grafts wet by spraying Ringer's solution over the grafted area.

We consider the following as indications for fixing grafts by the help of the fibrin-sealing system in burns:

1. Grafts over areas which are mechanically strongly affected by motion (face, joints, hands)
2. Grafts which are not meshed for cosmetic reasons
3. Grafting in children
4. Extensive grafted areas to avoid loss of skin
5. Mesh grafts on wound areas which are greatly endangered by bleeding or infection

Results

More than 90% of the area of the grafts we sealed by fibrin were accepted in most cases. Some grafts were taken totally. In three cases we lost about 50% of the grafts because of extensive infection. Of course it is very difficult to say whether the use of this rather expensive therapeutic material is of great advantage in the special case. Consequently in some cases we covered the wound ground by grafts which were sealed, whereas other grafts were only placed on the ground. During further necessary operations we then took small excisions out of the two areas grafted in these different ways.

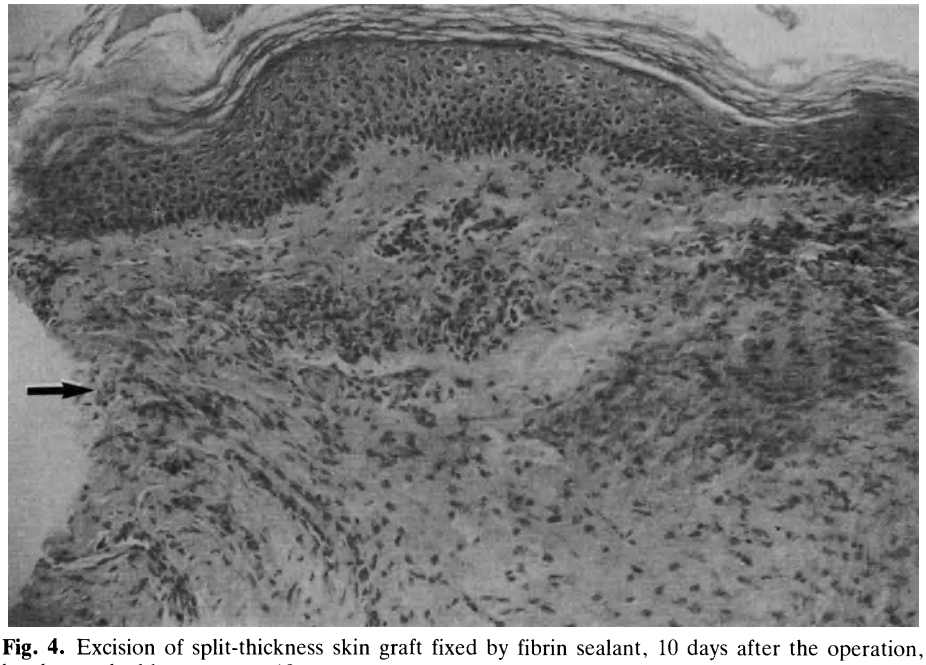

Fig. 4. Excision of split-thickness skin graft fixed by fibrin sealant, 10 days after the operation, border marked by *arrow*, × 10

The histological studies were carried out at the Institut für Pathologie der Berufsgenossenschaftlichen Krankenanstalten "Bergmannsheil Bochum", Bochum University, by Professor Dr. K. M. Müller. In some cases we could hardly find a difference between sealed and nonsealed grafts at the border of the ground. While we found stronger chronic-inflammatory reactions with perivascular edema and bleeding as well as perivascular round-cell-infiltration under the grafts which were not sealed, sealed grafts show very few pathological reactions in some cases (Fig. 4). A definite judgment is not possible at this point of the study, but to a certain extent these results seem to be in contrast to some animal studies.

We think that fixation of split-skin grafts within the operative treatment of burned patients by a fibrin-sealing system leads to a better proportion of accepted grafts.

Especially over areas which are mechanically stressed such as face, hands or joints graft-sealing seems to be indicated. Initial histological studies of sealed and non-sealed grafts may also give an argument for the fixation of grafts on burn wounds by a fibrin-sealing system.

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Fibrin Sealing in Dupuytren's Contracture

E. EIDE

Key words: Dupuytren's contracture, tissue sealing with Tissucol

Abstract

In the surgical treatment of Dupuytren's disease a tissue sealant, Tissucol, has been used rather than vacuum drainage to reduce postoperative haematoma formation. Tissucol has been used in more than 350 severe cases of Dupuytren's disease. The size of postoperative haematoma formation and the degree of wound edge necrosis have both been significantly reduced. An earlier return to function has been observed.

Introduction

Dupuytren's contracture is a disease of connective tissue and it normally affects the palmar aponeurosis. It can also attack the plantar aponeurosis and the penis and in the latter leads to the so-called induratio penis plastica.

Dupuytren's disease of the hands occurs in 1%–2% of the population predominating in about the 5th decade. The male-female ratio is 6 to 1 [1, 5]. The aetiology is unknown. Genetical factors seem to play a certain role and it occurs more frequently in patients with rheumatoid diseases, diabetes mellitus and cirrhosis of the liver due to alcohol abuse [3, 6, 8].

Pathological-anatomical swelling and disintegration of the collagenous fibres in the intercellular connective tissue lead to a cell proliferation from the perivascular area. The purpose of this reaction is to reduce the affected fibres and to create new ones. Because the fibre reparation and the production of cicatrice tissue proceed uncoordinatedly, the aponeurosis shows excrescences which reach from the paratendineum and the metacarpus bones on the one side to the dermal tissue on the other side. The flexor tendons are not attacked. Histologically you can find excrescences and fibroblastic cell formations. At a later stage the newly produced collagenous fibres shrink. The sebaceous and perspiratory glands atrophy [2, 4, 7, 9]. All these events lead to an increasing contraction of the fingers. How fast such a contraction develops is individually variable. Occasionally a hand can be completely contracted within a year while in other cases the contracture proceeds slowly over a period of more than 10 or 20 years. Usually the contracture starts with the fourth finger with a V-formed retraction of the skin and a light flexion in the proximal joint of the finger. Subcutaneously one can feel a thick cord of the palmar aponeurosis. In an advanced

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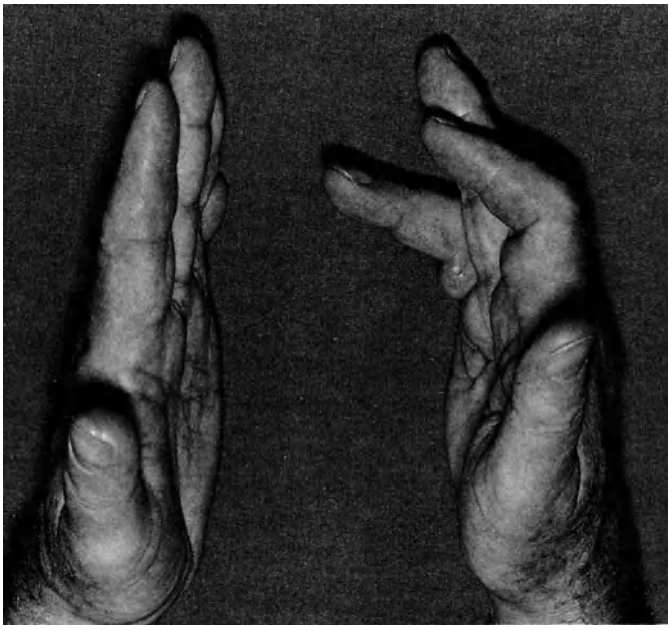

Fig. 1. Patient A, 69 years old. The left hand was operated on 8 months ago and had wound sealing with Tissucol. The right hand is shown preoperatively

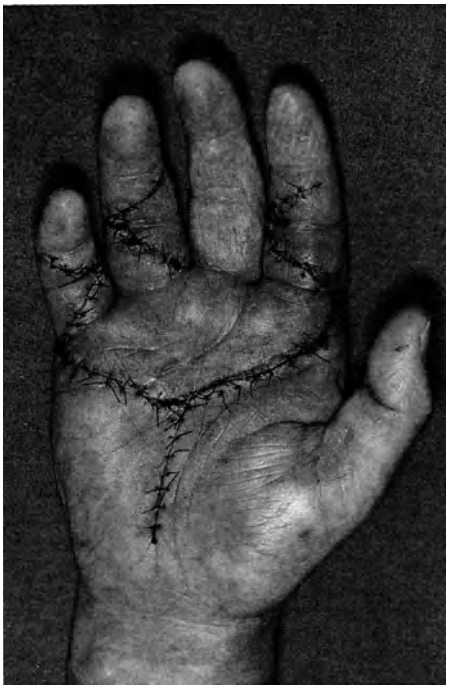

Fig. 2. Patient A. The right hand 24 h postoperative. The palm is slim, no haematoma formation, good vascularization and no vacuum drainage

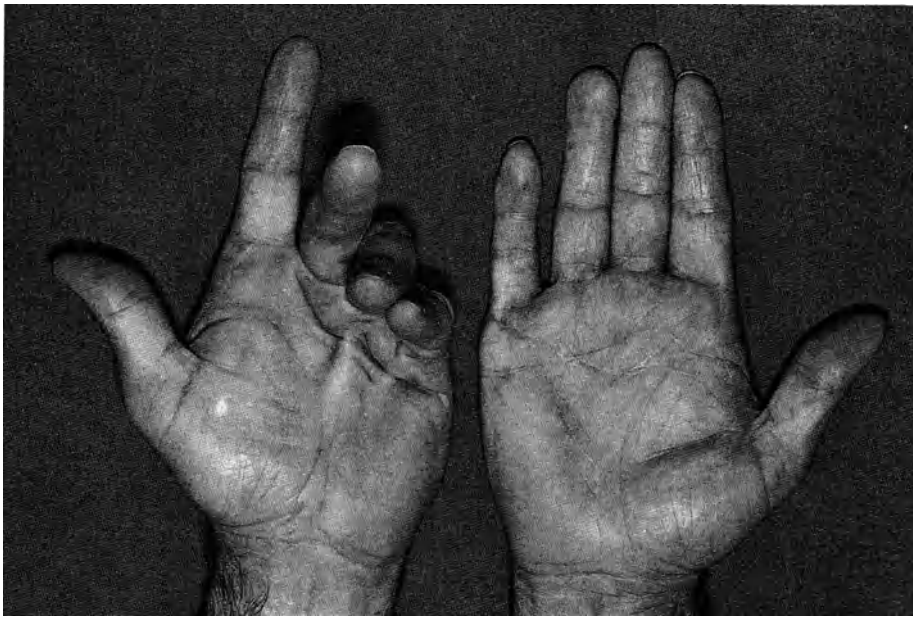

Fig. 3. Patient B, 52 years old. Aponeurectomy of the right hand, 1978. Repeat operation 7 months previously with wound sealing with Tissucol. The left hand is shown preoperatively

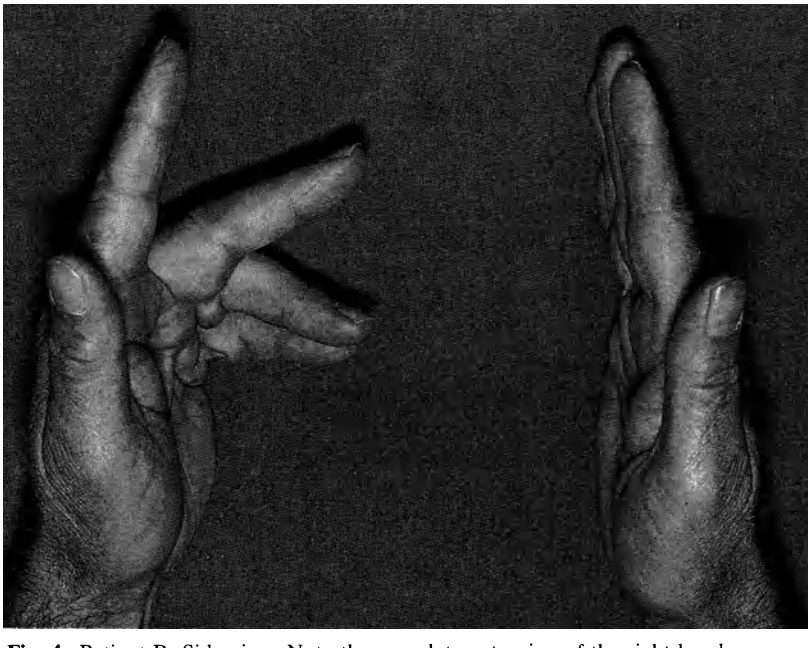

Fig. 4. Patient B. Side view. Note the complete extension of the right hand

case the normally smooth and elastic skin of the palm is totally coalesced to the palmar aponeurosis and in the skin folds of the palm one can see macerations of the skin [4].

The skin poses special problems during operative procedures for severe cases of Dupuytren's disease. This is because of its connection to the cords and because of the fibrous changes of the skin itself. When the skin is dissected from the cords, damage of the small vessels perforating the palmar aponeurosis is unavoidable. In this way the wound edges are undermined and the vascularization is reduced. As a result wound edge necrosis is possible and the vascularization is even more threatened by postoperative haematoma formation of the palm. Haematoma formation belongs to the more frequently seen and mostly-feared postoperative complications.

Since Dupuytren (1832), numerous operative methods and incisions have been described. We use different incisions depending on the extent of the disease. In the palm we use a Y-incision or a multiple Z-plastic incision or a combination of both of them. Furthermore we use zigzag incisions on the fingers. These incisions allow an exact preparation of the palmar aponeurosis and the cords, which is very important for the preservation of the nerves and vessels. Until May 1981 we used vacuum drainage for 2 days after the aponeurectomy. These drainages were often plugged by

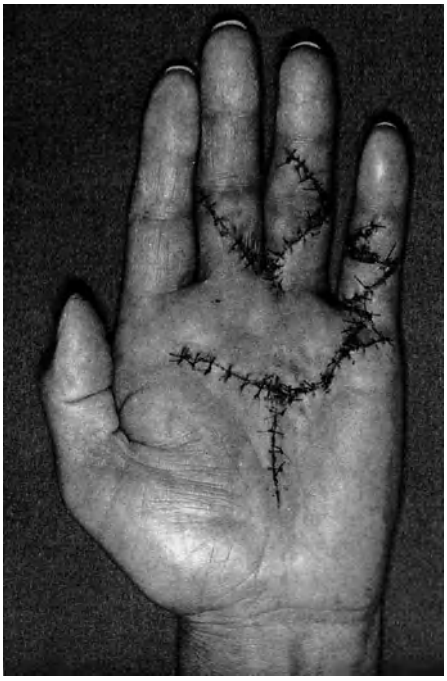

Fig. 5. Patient B. 13 days postoperative. No haematoma formation. Only minor wound edge necrosis. It was possible to make a primary suture over the proximal joint of the fifth finger with a "Z-rectifie"

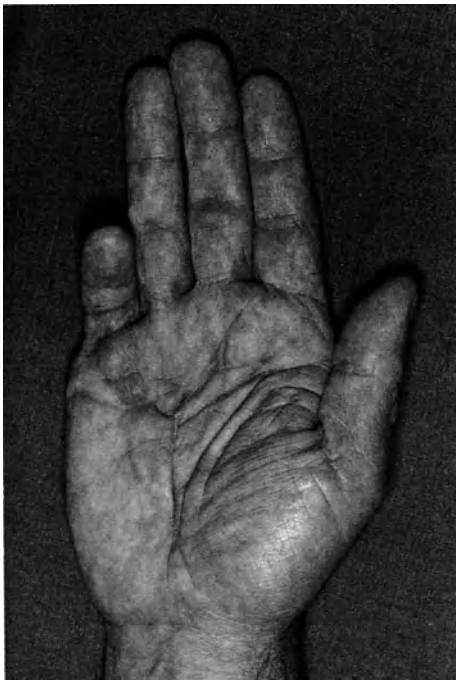

Fig. 6. Patient C, 61 years old. Recurrence after an aponeurectomy 1 ½ years previously

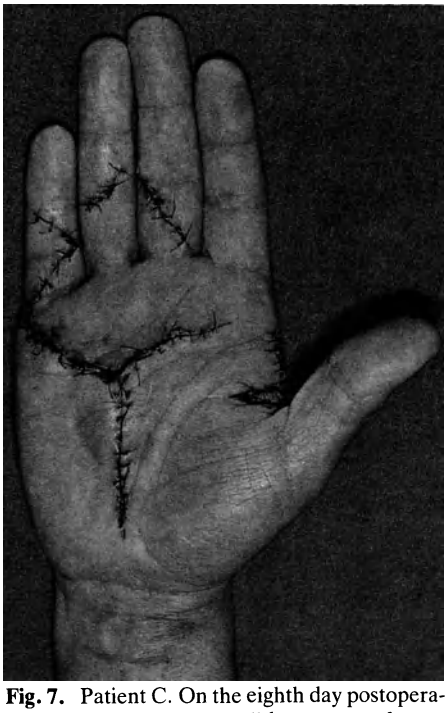

Fig. 7. Patient C. On the eighth day postoperative day we can see a small haematoma formation in the palm

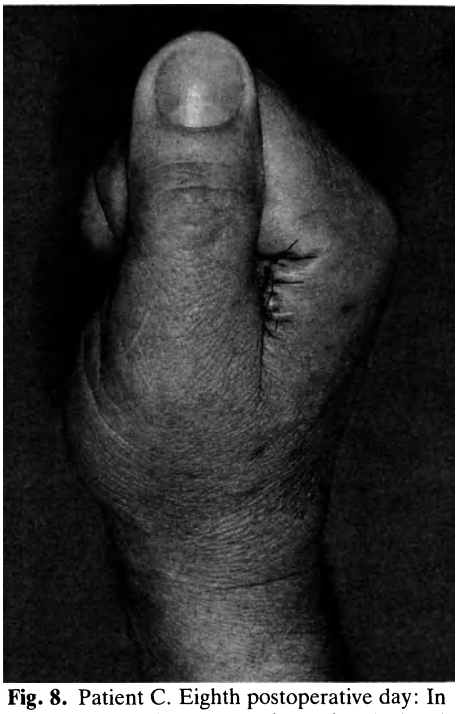

Fig. 8. Patient C. Eighth postoperative day: In spite of a minor haematoma formation the hand shows very food function

small blood clots, and despite the drainage extensive palm haematoma occurred. If this happened a wound revision was necessary, the infection risk rose and wound healing was impaired. In May 1981 we tried the tissue sealant Tissucol instead of using vacuum drainage. The first experiences were so encouraging that since then we have used Tissucol in every operation of Dupuytren's disease. No vacuum drainage has been necessary.

Method

After the aponeurectomy the wound is sutured as usual with single sutures. Then Tissucol is used in the so-called premixing technique. The components are mixed in a small bowl and drawn into a disposable syringe. Using a button cannula we then inject the sealant into the wound. This is possible only when using the "slow solidification", e.g. a thrombin concentration of 4 IU/ml. Thereafter the wound has to be compressed for 5 min in order to achieve a sufficient attachment. A compressing bandage is applied before we loosen the pneumatic blood tourniquet and the hand must be elevated for the duration of the reactive hyperaemia. For a normal aponeurectomy we need 2 ml Tissucol; for minor findings 1 ml would be enough. On

the third postoperative day the patient starts with active exercises, still keeping the dorsal underarm cast.

Results and Discussion

Since 1962 Dr. H. Jurgeit has been in charge of hand surgery in the St.-Jürgen-Straße Hospital. This paper is a result of the author's experience during training in this hospital in association with Dr. Jurgeit. He has performed more than 2000 operations for Dupuytren's disease and out of these more than 350 have been carried out with additional wound sealing with Tissucol. Since the introduction of Tissucol we have observed that the development of wound edge necrosis has been definitely reduced, especially with multiple Z-plastic incisions on several fingers. It seems that we have achieved a faster revascularization of endangered areas by using the fibrin sealant.

We had the chance to make a retrospective analysis of the first 187 cases with Tissucol and the last 100 cases carried out with vacuum drainage. It showed that the frequency of postoperative palm haematoma formation was the same in both groups. However, when using the fibrin sealant the size of the palm haematomas was reduced and they were only 2–3 cm in diameter. These small haematoma formations were almost negligible and seldom required a second operative procedure. The degree of wound edge necrosis was significantly reduced possibly due to a faster revascularization. Of the 187 cases treated with Tissucol we had to make a secondary suture in only two of them. In the comparative group with 100 cases we registered six secondary sutures and two skin grafts. It is important to point out that we mainly treat severe cases of Dupuytren's disease, also recurrent cases with complicated conditions. Nevertheless we do not make any primary skin grafts or advanced flaps.

We saw the most haematoma formations when using the Y-incision for the palm and they often occurred on the third or fourth postoperative day. This might depend on an individual faster resorption of fibrin. During the period from May 1981 to April 1985 we observed no change in the rate of recurrences. We also observed no infections while using Tissucol. As mentioned before, the patient starts with active exercises on the third postoperative day. In order to obtain a good function at an early stage we consider physiotherapy to be very important. We observed an earlier return to function of the hand when using the fibrin sealant although this could not be proved.

Altogether the rate of postoperative complications has been reduced since we started using the fibrin sealant Tissucol instead of vacuum drainage. For this reason we find the higher costs using the fibrin sealant absolutely justified.

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Fibrinogen Glue (Tissucol/Tisseel) Skin Transplants in Leg Ulcers

J. HOLM

Key words: Leg ulcers, arterial, venous, fibrinogen glue

Abstract

In patients with leg ulcers, of both arterial and venous origin, it is an advantage if the ulcers are healed before a definitive treatment is attempted. Most venous ulcers heal with an adequate compression therapy but this is often time consuming. Regarding arterial ulcers, healing is difficult to achieve before reconstructive vascular surgery but is preferable in order to reduce the risk of postoperative wound infections. Tisseel, a commercially available fibrinogen glue, offers a new possibility to achieve ulcer healing in these patients. Fifty patients, 40 with chronic venous ulcers and 10 with arterial ulcers, were treated. Split-thickness skin grafts were taken in local anesthesia and glued to the ulcers using Tisseel. The treatment was performed on an outpatient basis. In 32 of the 40 patients with venous ulcers and in 5 of the 10 patients with arterial ulcers, the skin transplant remained viable and the period to complete healing was thus greatly reduced. A healed leg ulcer reduces the risk of wound complications after reconstructive arterial or venous surgery. Split-thickness skin transplants can be used with an ordinary technique but this is an expensive method since it usually requires hospitalization. Gluing of skin transplants with Tisseel seems to be a good alternative and has the advantage that it can be used on an outpatient basis.

Introduction

Leg ulcers are frequent and cause discomfort for the patients and consume a lot of resources for the health services [1]. Thus in Göteborg, Sweden, a town of less than half a million inhabitants, more than 20 000 hospital days were taken during 1980 for patients with leg ulcers. The leg ulcers are mainly of venous origin although, at least in Sweden, the proportion of arterial ulcers has increased substantially over recent decades from about 1:9 to about 1:3. Leg ulcers are symptoms of an underlying disease and thus the treatment is symptomatic and recurrences are very common if the underlying disease has not been or cannot be treated. Regarding venous ulcers there is usually an underlying deep venous insufficiency or a postphlebitic syndrome and correspondingly in arterial ulcers an arterial occlusion of iliac or femoral arteries. It is preferable if the leg ulcers are healed before the definite treatment of the underlying disease is attempted. This can usually be achieved in venous ulcers

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with an adequate compression therapy [2,3]. In arterial ulcers, where the nutrition of the skin is insufficient due to a decreased arterial blood flow, it is much more difficult to get the ulcer to heal before the arterial occlusion is removed by vascular surgery. Nevertheless the risk for wound infections is greatly reduced if the leg ulcers are healed at the time of definitive surgery. The aim of the present study was to see if healing could be obtained with gluing of skin transplants to the ulcer area.

Material

Fifty patients with chronic leg ulcers are considered; 40 had venous ulcers and 10 had arterial ulcers. The mean age was 74 years in the group of patients with venous ulcers, with a predominance of females. The mean age in the group of patients with arterial ulcers was 72 years, where there were more males. The ulcers were located to the lower leg or the foot and in no instances were larger than 5 × 5 cm.

Method

The patients were treated on an outpatient basis with dressings once or twice per week. The ulcer treatment was the same in both groups, i.e., a careful debridement and cleaning of the ulcers in surface anesthesia using a lidocaine gel (Xylocaine gel, Astra). In appropriate cases systemic antibiotics, usually penicillinase stable penicillins, were used. In patients with venous ulcers and with an ankle pressure of more than 80 mm-Hg, double compression bandages were used. An inner bandage containing zinc oxide (Quina-band, Seton) was used and around this an elastic adhesive bandage was wrapped. In arterial ulcers a Vaseline gauze containing an antistaphylococcic antibiotic (Fucidin, Löwens) was used. When the ulcers were clean, free of infection and showing red, granulating tissue in the bottom layer, a split-thickness skin graft was taken in local anesthesia from the thigh, meshed and glued to the ulcer area with the Tisseel spray. The fibrinogen part of the Tisseel was reconstituted with an aprotinin solution to avoid early fibrinolysis. The freeze-dried thrombin was dissolved in calcium chloride solution according to the instructions on the Tisseel kits. When these two components were mixed a fast formation of fibrin occurred which had good adhesive properties. The patients were given suitable bandages and sent home. Three days later the patients came back to the hospital, the bandage was changed to a new one and after that day the dressings were changed once a week until healing of the ulcers. The procedure of skin grafting was thus simple and quick and usually three or four patients could be treated in this way within an hour. No untoward effect of the fibrin sealant was seen.

Case Report

A 77-year-old male with a leg ulcer of combined arterial and venous origin. Despite successful arterial reconstruction the ulcer just above the ankle would not heal (Fig. 1). A split thickness graft was glued to the ulcer area and healing was quickly achieved (Fig. 2).

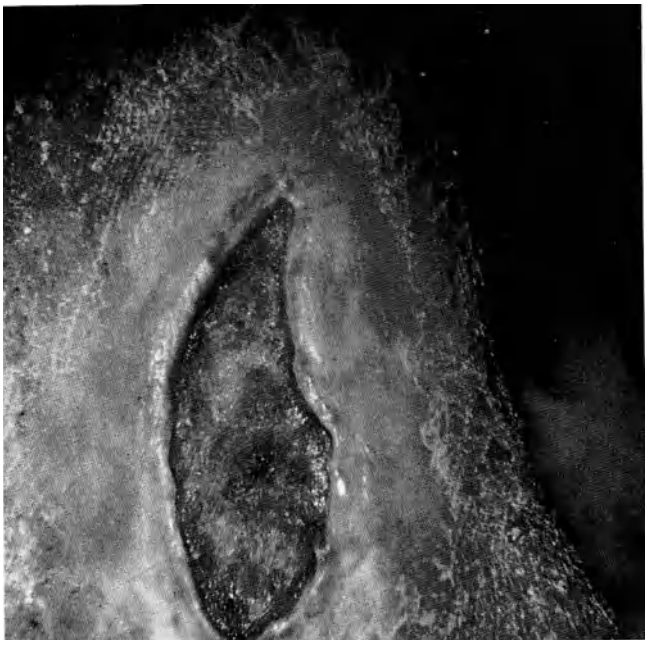

Fig. 1. Leg ulcer just above the ankle 1 year after arterial reconstruction

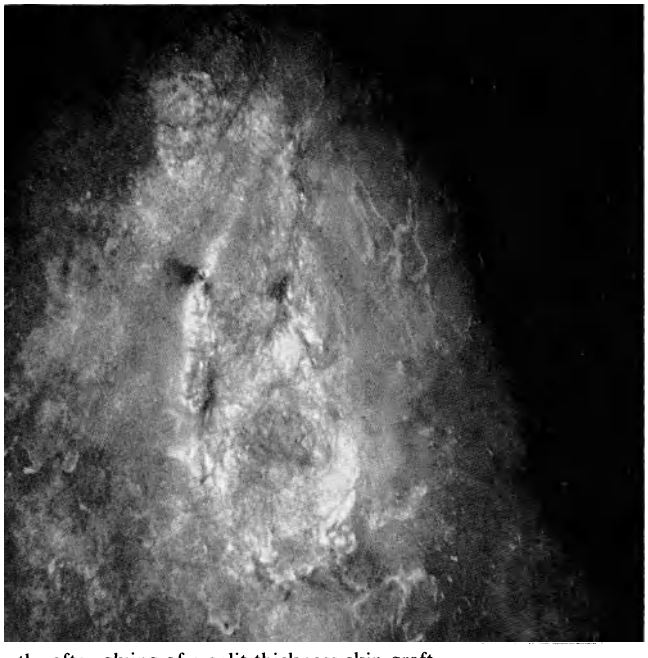

Fig. 2. Healed leg ulcer 2 months after gluing of a split-thickness skin graft

Results

In 32 of the 40 patients with venous ulcers and in 5 of the 10 patients with arterial ulcers the skin graft "took" wholly or partially. If the skin transplant was only a partial success, it was our impression that the rest of the ulcer area showed an increased tendency to heal for a few weeks after the Tisseel spray had been put on. In the remaining cases there was a lysis of the skin transplant which became unviable. This was evident after the first 3 days in most cases.

Discussion

Gluing of skin transplants with Tisseel is a valuable adjunct in the treatment of leg ulcers [4]. There are two possible explanations for this:

1. Tisseel in itself seems to be a stimulus for healing of skin ulcers, maybe because of its content of fibronectin and other growth factors [5].
2. A skin transplant glued with Tisseel is firmly adherent to the ulcer area for at least 3 or 4 days before fibrinolysis takes place, provided that an aprotinin is used as a fibrinogen solvent, thus counteracting the fibrinolysis.

During this time budding of new microvessels into the skin transplant can take place. Most leg ulcers of venous origin heal without skin transplants but this usually takes a very long time. Split-thickness skin transplants using the ordinary technique with stitching of the graft to the ulcer area requires hospitalization for a week or two and is therefore a very expensive method. With Tisseel it is possible to do the skin transplant as an outpatient procedure, thus saving hospital beds. Thus in two-thirds of the patients with venous ulcers and in half of the patients with ischemic ulcers of arterial origin, it was possible to get the patients free of skin ulcers before the definite treatment was attempted. This is worthwile since a healed leg ulcer reduces the risk of wound complications after reconstructive arterial or venous surgery. With increasing experience of the gluing procedure and with adequate pretreatment of the leg ulcers the success rate of gluing has increased.

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New Aspects of Haemangioma Treatment

A. KRÜGER

Key words: Haemangioma, Tissucol

Abstract

This paper deals with the successful therapy of cavernous and capillary haemangiomas through the forming of thrombosis with fibrin sealant (Tissucol). With infants and small children after angiography, every 2 weeks Tissucol was injected directly into the vessel convolution, which led to a total thrombosization with subsequent fibrosis and trituration until the haemangioma gradually wasted away, causing an eventual annihilation of the haemangioma.

Histological investigations showed fibrosis and/or sclerosis of granulated tissue enriched with fibroblasts, representing a partially organized thrombosis. There were signs of inflammation. With many adult haemangioma patients the diminution of the haemangioma through Tissucol injections led to thrombosis and an immediately subsequent total extirpation of the whole haemangioma.

The treatment of smaller haemangiomas with cryosurgical measures with liquid nitrogen dioxide was carried out successfully.

Introductory Notes

Haemangiomas with mainly capillaries often disappear spontaneously, whereas those with more cavernous vessels can persist due to a strong destructive burrowing activity; these need treatment.

Earlier attempts to achieve obliteration by compression did not succeed (Bell). In 1981 Lexer recommended total excision and cauterization with smoking salpeter acid as well as the pricking of the tumour with magnesium injection, as Payr did for subcutaneous angioma of the scalp and face.

Injections of chemical substances (e.g. 70% alcohol, 1% chlor-zinc-solution) led to scabbing and necrosis, but also to bleedings and inflammations; even bleedings to death have also been reported. Application of frozen carbonic acid was carried out by Sauerbruch. The radiation therapy mentioned in the same report is nowadays considered to be obsolete.

In 1954 Dennecke and Hartert wrote that the injection of thrombin into vessels in a case of permanent nosebleed was successful: An improvement of the above-mentioned technique, namely thrombin injected into the vessels, can probably be achieved by a simultaneous injection of a solution containing fibrinogen with the

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thrombin solution. Hereby, through an increased concentration of the fibrinogen in a selected place significant coagulation might be achieved.

Procedure

The idea and the technique of selective and superselective embolization when carrying an embolizing substance through a catheter are also applied to a vessel tumour preparatory to the operation. I applied Tissucol (fibrinogen and thrombin) directly into a tumour for the first time 5 years ago.

Fibrin glue (Tissucol) is human fibrinogen and thrombin that are injected from two syringes in a Y-form and immediately unite into a gelatinlike body (mass). At the moment of injection, the injected Tissucol unites with the fibrinogen and the thrombin contained in the blood into a thrombus which wholly fills the anginomatously widened volume of the vessel.

I then use the hardening phase of Tissucol. The injection takes place without a local anaesthetic and each time directly with a needle into the depths of the haemangioma. With infants and small children, and with patients where no operation is intended or planned, the Tissucol injection can be repeated at 3 weekly intervals. This procedure leads to a clearly progressive decrease of the amount of blood in the vessel tumour. The proportion of the connective tissue increases; the haemangioma shrinks. With adults and children who were going to be operated on, due to the shrinking of the tumour an unproblematical extirpation could be carried out.

Treatment with injections should always be preceded by angiographic presentations of the tumour in order to explain the to and fro movement of the flow.

Presentations of Certain Cases

1. This patient (Fig. 1) is a 2-year-old baby girl with a very big swelling above the skin level, a haemangioma located exactly over the fontanelle. The tumour had been growing considerably during the previous months and was bleeding. Due to the strong pulsation it had to be found out whether the tumour was being nourished intracranially or extracranially. Filling took place through the arteria temporalis from both sides. The Tissucol injection led to an exceptional decrease of the amount of blood in the tumour so that an unproblematical total extirpation could be carried out.
2. The first injection of Tissucol into the depths of a haemangioma was made in a 4-month-old infant in 1980, whose haemangioma of the upper lip was erosive and was bleeding daily (Fig. 2). There was rapid increase in the swelling of the haemangioma; the result was a middle defect of the entire upper lip; the haemangioma grew on to the bridge of the nose and became inflamed. As the child could not be fed by breast or by bottle, it had to be nourished with a tube. Repeated injection led to stoppage of the bleeding, decrease of the inflammation and the closing up of the defect in the upper lip region. The child is now 5 years old and has not yet been operated on. The haemangioma has disappeared. Later on a correction of the upper lip scar will be carried out (Figs. 3, 4).

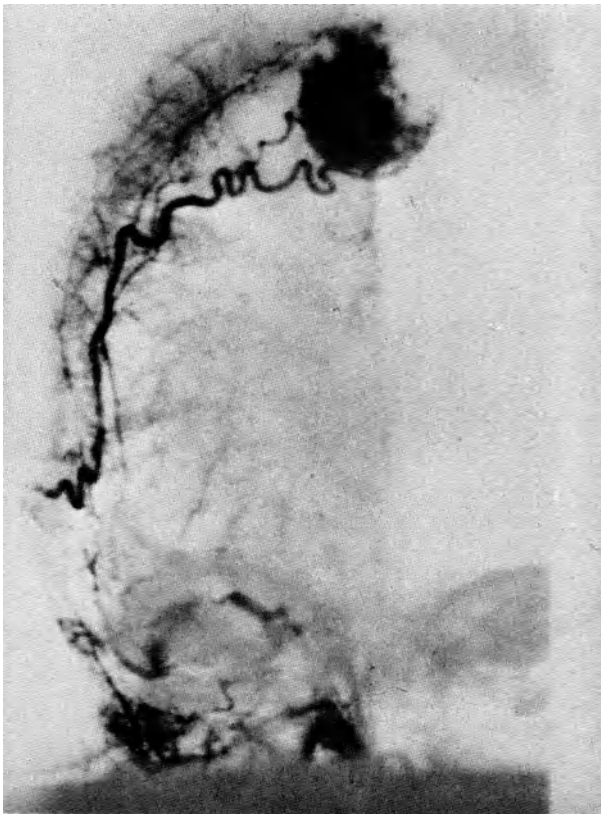

Fig. 1. Angiography of a haemangioma over the fontanelle in a 2-year-old baby girl, nourished from the arteria temporalis

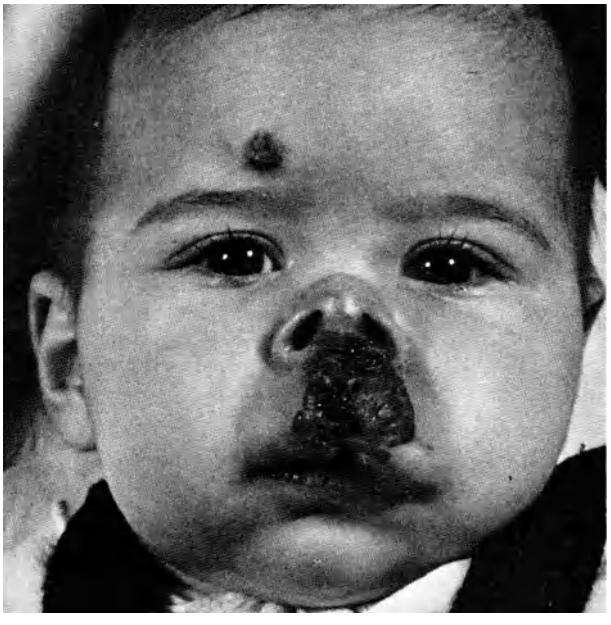

Fig. 2. Spreading, bleeding haemangioma of the upper lip of a 5-month-old infant

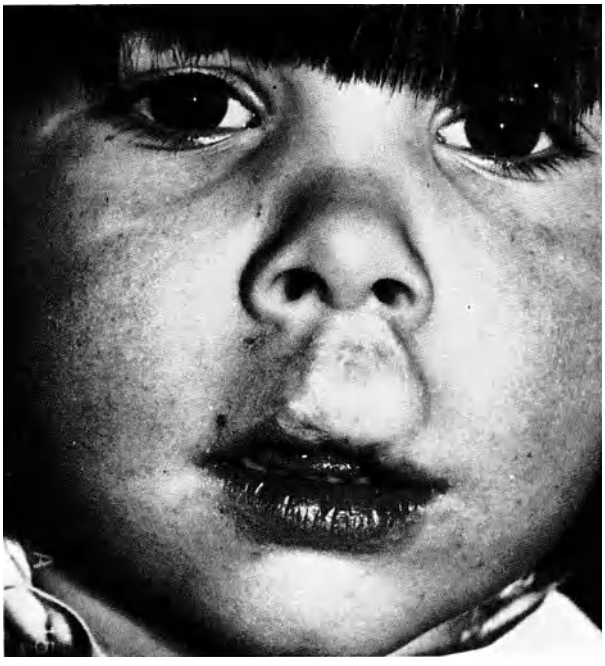

Fig. 3. State of the scars of the upper lip after Tissucol injection. Present state of the now 4-year-old girl. Up to now no operation of any kind has been performed

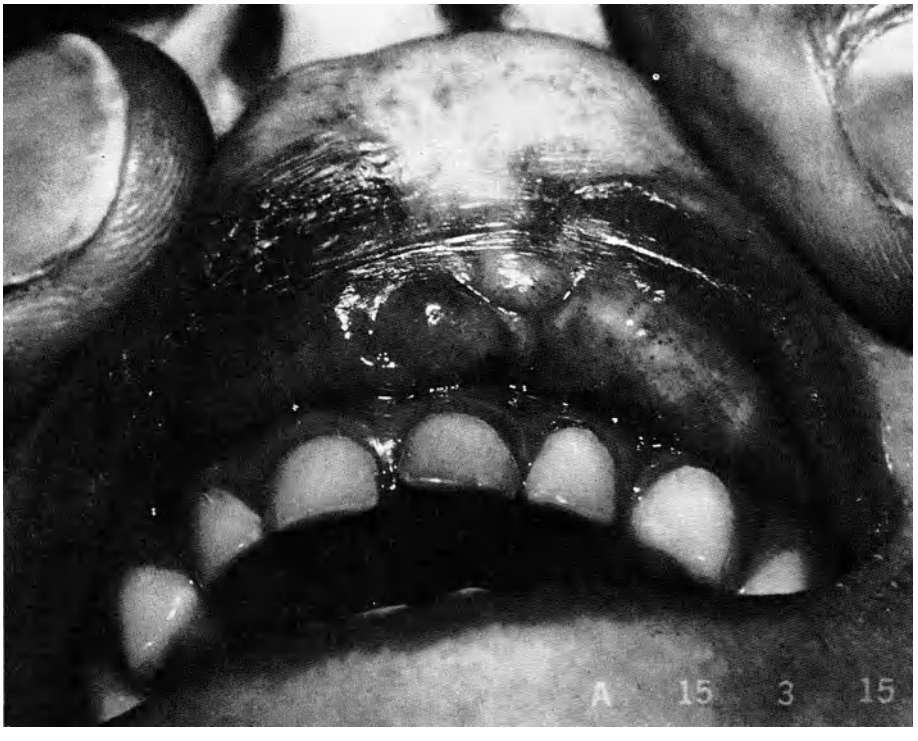

Fig. 4. Upper lip mucous lining, free of haemangioma in the same now 4-year-old girl (state after Tissucol injections – human fibrinogen and thrombin)

Histological Results (Figs. 5, 6)

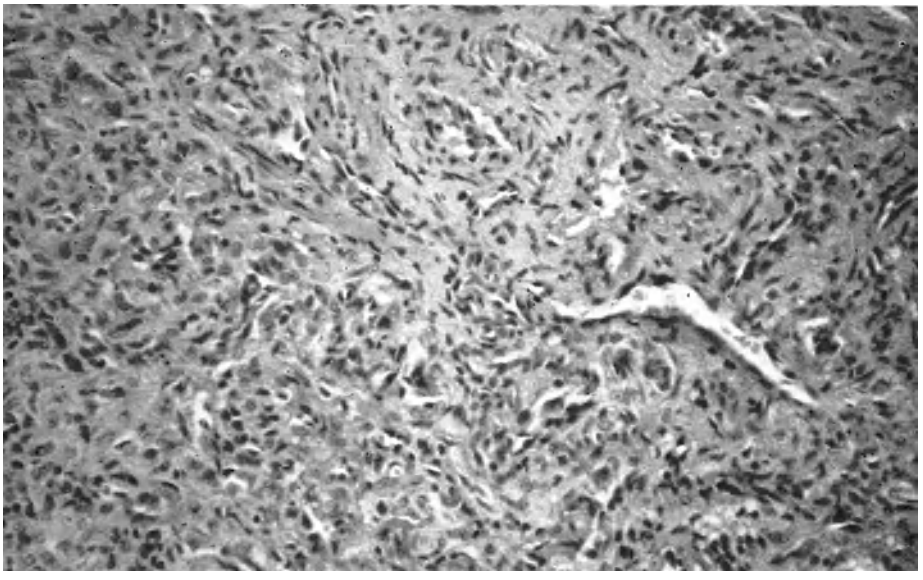

Fig. 5. Cavernous haemangioma with widespread sclerosis and partial thrombosis after repeated fibrin glue injections with distinct fibrosis or sclerosis respectively. In some places thin patches of cavernous vessels are recognizable with quite a lot of fibrinoblastic granulated tissue in the centre, as the expression of partially organized thrombosis – no signs of inflammation

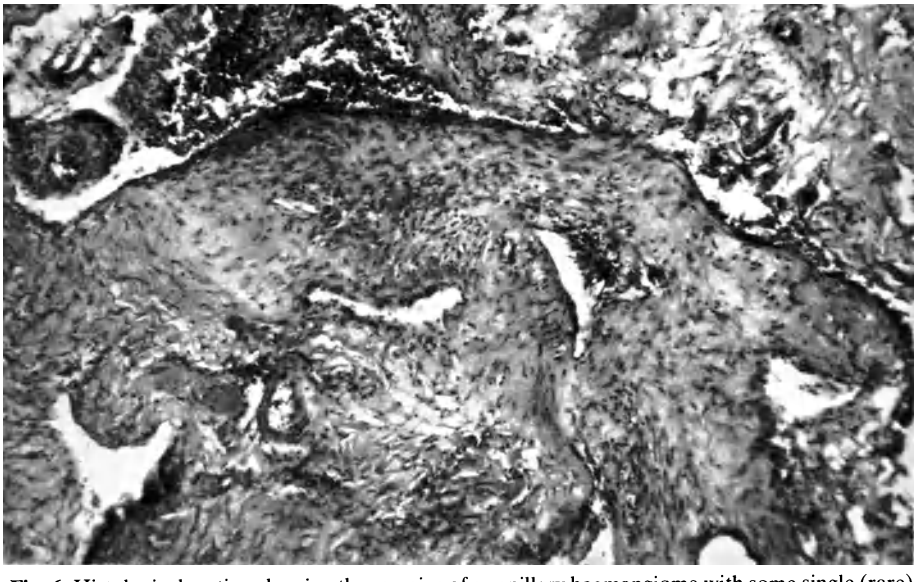

Fig. 6. Histological section showing the remains of a capillary haemangioma with some single (rare) angiomatous light capillary patches and clearly predominant fibrosis. In the coloured connective tissues the faint vessel remains are only barely recognizable. There are no signs of inflammation

Cryosurgery

A further aspect of haemangioma treatment was recommended by Lexer and von Bergmann in 1921; treatment with cryosurgical measures for congealing and obliteration. For this purpose small haemangiomas or remains of haemangiomas as well as pieces reduced by fibrin glue may be suitable. The icing is carried out by spraying liquid carbon dioxide onto the surface of the haemangioma. This treatment may be repeated in the outpatient department every 3 weeks.

Combination of Treatments

In the combination of both types of treatment I see a certain advantage:

1. In all those cases where a haemangioma is not going to be operated on; the increasingly rapid growth is held up through the reduction of the amount of blood by fibrose. On several occasions no operation was necessary
2. The haemangioma destined for extirpation can be totally thrombosized by Tissucol injections, whereby an exact and reliable isolation and a blood- and tissue-saving preparation can be achieved. Thus complete extirpation is carried out and residues of haemangioma are avoidable.

Discussion

The thrombosis achieved through obliteration and organization after Tissucol injection leads to the hemangioma shrinking. As the application of the rapidly hardening phase of the fibrin glue at the moment of the injection, together with the thrombin and the fibrinogen in the blood, turns it into a tightly fixed thrombus, the danger of embolism by the thrombus moving on is improbable from a pathophysiological point of view.

Should the angiography show voluminous draining off, previous disconnection of the large vessels is possible in such cases. In all the cases of angioma treated with thrombosis by the author such measures were not necessary.

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III. Maxillofacial and Dental Surgery

Use of Tissucol (Tisseel) in Maxillofacial Surgery

G. Ferrari Parabita, G. Derada Troletti, and R. Vinci

Key words: Fibrin glue, maxillofacial surgery, Tissucol

Abstract

Fibrin glue (Tissucol) is a biological substance derived from human donor plasma by means of cryoprecipitation, producing a highly concentrated solution of fibrinogen and other cryoglobulins. This fibrinogen contains the coagulation factor XIII and in the presence of both thrombin and calcium is a filamentous precipitate of highly adhesive fibrin. In this paper we present the mode of action of Tissucol and its method of preparation. We also present and discuss the way in which Tissucol effects tissue repair and the effectiveness of fibrinogen in this process. The indications for proper use of Tissucol are a consequence of this healing process and we report on the use of Tissucol in maxillofacial surgery in tegumentary lesion repair, in plastic surgery and in bone surgery.

Introduction

Tissucol is a biological and adhesive material with two components. In addition to its adhesive properties, it permits immediate haemostasis and favours repair processes in damaged tissues. The Tissucol consists of freeze-dried fibrinogen (Tissucol), a product containing coagulable human plasma proteins, and freeze-dried thrombin as well as aprotinin and calcium chloride, which are used to reconstitute the freeze-dried Tissucol and thrombin respectively. Appropriately mixed the various components solidify into a strong plasma coagulum. Lysis of the coagulum is delayed by adding aprotinin so that the fibrin reticulum formed stimulates the proliferation and growth of new fibroblasts. The fibrin glue formed in this way has triple action: it is adhesive, haemostatic and stimulates tissue repair. The biological properties of Tissucol make it suitable for various operations on the maxillofacial area. It is particularly useful in: reconstructive surgery since it stimulates the adhesion and tissue repair of: skin flaps, myocutaneous flaps, skin grafts, and bone grafts. Being both haemostatic and adhesive, it can also be used in microsurgical nerve suturing and vascular anastomoses. It facilitates the knitting of bone grafts and the formation of the bone in osteotomies and is therefore useful in the surgical correction of dental and facial deformities. In injuries to the skull, jaw and face it can be usefully applied to fractures; especially highly fragmented and comminuted fractures. The haemostatic action of Tissucol prevents haemorrhagic complications in patients with haemophilia, liver disease, and anticoagulation treatment.

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Case Histories

Case 1

Our first case is a 17-year-old girl with massive recurring fibrous dysplasia in the right mandible. The patient had already undergone plastic surgery at the ages of 9, 10, 12 and 14 years. The smooth, hard, painless swelling stretched from the right corner of the mandible to the left paramedian region. The mouth opening was normal with a lateral deviation of the mandible inside the mouth; the mandible occupied and deformed the vestibular and gingivolingual fornix.

Current and earlier panoramic X-Ray and computed tomography showed the horizontal ramus of the right mandible to be much enlarged; the cortical area was preserved and the tumour was found to vary in density. Since conservative plastic surgery failed, we opted for a radical approach: excision of the tumour and immediate reconstruction using an iliac bone graft.

The first step was to make an incision into the para-alveolar mucosa, to detach the mucoperiosteum of the mandible. The left vessel-nerve bundle was drawn back to preserve it entire. Extraoral fixations were used to stabilize the rising ramus of the mandible. Osteotomies were then performed at the right corner of the mandible between the first and second left bicuspid. The muscle insertions on the floor of the mouth were cut and the tumour removed. Anatomical and histopathological examination of the tumour showed a bone matrix organized in irregular bundles with often incomplete areas of calcification. Dense patches of fibrous connective tissue were found between the bone trabecule. We reconstructed part of the mandible using an iliac bone graft. The two fragments, 14 cm long in all, were shaped and divided into three segments. These were joined by a double wire loop and fibrin glue. The shaped bone graft was then wired to the residual mandibular segment. The muscle of the mouth floor and the jaw-lowering muscles were inserted through drills in the graft and fixed with nonadsorbable suture. Before double-layer suturing periosteum and mucosa we used more fibrin glue for haemostasis, sealing and adhesion. We also found that the fibronectin of the Tissucol stimulates the growth of osteoblasts while the fibrin itself is necessary for the growth and spatial arrangement of the collagen.

A specially made and appropriately remodelled prosthesis and steel perimandibular and perizygomatic loops were then applied to contain the bone. There were no postoperative complications or local infection or dehiscence of the mucosa. Radiological X-ray showed the jaw and graft well aligned in all three directions.

Case 2

Our second case is an 18-year-old patient with secondary deformity of monolateral right cleft-lip-palate. This included retrusion of the maxillary with transversal displacement and prognathism. After clinical cephalometric examinations we decided to move the maxillary forward while at the same time applying a graft to the alveolar cleft and performing a sagittal osteotomy on the mandibule. We began with bilateral osteotomy of the mandibule. Next we performed a Le Fort I osteotomy of the maxillary. The pterigoid plates were then carefully detached from the tuber of

the maxillary by a thin, curved osteotomy. The segments of the maxillary were fractured and mobilized. The floor of the nose was closed by suturing the mucoperiosteal flaps of the lateral wall of the nose and the septum. Further osteotomies were used to control the various cuts in the jaw. We separate the segment without damaging the vessel-nerve bundle; and then we insert a splint, applied on intermaxillary fixation. In order to favour the development of the new bone and stabilize the mucoperiosteal flap, fibrin glue was also applied around the bone graft, to prevent the displacement in the alveolar cleft and pterigomaxillary space.

Case 3

Our third case is a 54-year-old patient with a carcinoma on the right cheek and mandibular gingiva with suspected metastasis to the right jugodigastric region. The patient had already been given radiation treatment because he refused surgical treatment. Then he suffered a recurrence and a neoplastic infiltration appeared in the skin and mucosa of the cheek (Fig. 1). We began with radical neck dissection; after a modified Semken incision of the skin we prepared the upper, anteroinferior and posterior skin flaps. The underlying principle of neck dissection lies in the radical excision of the entire neck lymph system since this is already or due to be invaded by the cancer. All the fat and connective tissue of the neck, containing the lymph nodes and vessels, were removed. Wherever technically possible this should be done in all cancers of the head and neck when the primary tumour is removed. This is the rational and safe approach to tumour surgery since regional surgery

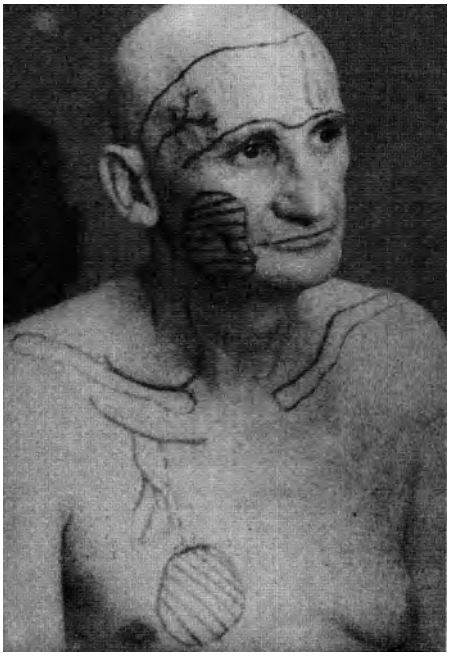

Fig. 1. Case 3, a 54-year-old patient with a carcinoma of the right cheek and mandibula gingiva with suspected metastasis to the right jugodigastric region

Fig. 2 u. 3. Removal of the portion of the cheek with the tumour, half mandible and submandibular laterocervical region of the neck in a single piece

should never be confined to the cancer area itself. After ligature and separation of the interior jugular vein near the base of the skull and dissection of the upper insertion of the sternocleidomastoid muscle we proceeded to remove the tumour, extra- and intraorally. Then we resected the mandible at the mental canal; in this way we removed the portion of the cheek with the tumour, half mandible, and submandibular laterocervical region of the neck in a single piece (Figs. 2, 3). For the reconstruction of the skin-cheek, we used a myocutaneous flap from the pectoralis major supported by the pectoral artery, a branch of the thoracoacromial artery; the flap consisted of an isle of skin and its underlying greater pectoral muscle. This flap is particularly appropriate for use in radical neck dissection since it protects the vessel and nerve bundle on the neck. Before the preliminary closure of the donor site we coated the area with fibrin glue.

A combination of traditional suture with fibrin glue gives closure and there is less risk of haematomas forming below the sutured flaps of the primary defect. For the reconstruction of the mucosa in the cheek, we used a McGregor flap with axial vascularization taken from the frontal branch of the superficial temporal artery. This flap provides enough tissue to reconstruct wide areas of exeresis; necrosis is rare and it provides extremely vital, hair-free skin that adapts easily to folds. For all these reasons and despite criticisms that may be levelled on aesthetic grounds, it is ideal for reconstruction after exeresis in the oral cavity (Fig. 4). We covered and protected the patient's oral cavity with skin graft from his leg. In this particular application the haemostatic and adhesive qualities of fibrin glue are extremely

Fig. 4. Reconstruction after exeresis in the oral cavity

valuable in attaching the graft. Furthermore the fibronectin and factor XIII in Tissucol make for better knitting between the graft and the receiving area, since both promote fast revascularization. Very few suture stitches were needed round the graft. The distal end of the frontal flap was rotated and placed inside the mouth. Passing under the zygomatic arch we sutured it carefully to the remaining mucosa, the pharynx, the floor of the mouth and the lip. We applied fibrin glue to enhance the adhesion between the cut surfaces of the frontal and myocutaneous flaps. Apart from its adhesive properties, the haemostatic qualities of Tissucol help prevent haemorrhages of the small blood vessels and the creation of haematomas below the flaps. A transfixion suture ensured the perfect attachment of the two flaps; finally we sutured the entire wound.

Conclusions

Our clinical observations and our reading of the literature have convinced us that fibrin glue offers a real advantage for the patient and is to be recommended as an alternative or better as a valuable addition to traditional suturing. One specific advantage of Tissucol in reconstructive surgery is its ability to provide immediate adhesion of the skin flap to the underlying tissue. In fact Tissucol is recommended whenever the area being covered offers incomplete guarantee of adhesion. Furthermore the adhesive property of the fibrin prevents the graft being detached by a haematoma at an early stage. Where the underlying tissue is swollen, Tissucol can be used with advantage, since the presence of α-2 macroglobulin and fibronectin gives it antiphlogistic properties.

In bone surgery, too, Tissucol is an ideal aid to the repair processes which it does not alter but even accelerates in the early stages. In conclusion we found Tissucol perfectly well tolerated when used as a biological glue on a variety of tissues and it helped us obtain satisfactory results in many areas of maxillofacial surgery. If precise indications are followed and indiscriminate use is avoided, Tissucol is a valuable and effective aid that simplifies and improves innumerable surgical techniques.

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New Methods of Fibrin Sealant (Tissucol/Tisseel) Application in Maxillofacial Surgery: The Use of Hydroxyapatite in Association with Human Fibrin Glue in Reconstructive Surgery

G. Ferrari Parabita, G. Derada Troletti, and U. Zanetti

Key words: Fibrin glue, hydroxyapatite, maxillofacial area

Abstract

Several ceramic compounds of calcium hydroxyapatite have been produced in the past 10 years and appear to offer hitherto unknown properties in terms of chemical composition and histocompatibility. The compounds, currently only marketed in a granular form, may be used in place of autologous bone grafts since they are biocompatible and also present no peripheral fibrous sulcus or conductivity. When mixed with fibrin cement the product has been found to have an even wider range of applications and has proved useful in oromaxillofacial surgery (to augment atrophied alveolar crests, in reconstructive surgery and in the surgical treatment of large cystic tumors). Histochemical and physical assessment of in vivo fragments confirm the properties of this new biological material.

Introduction

Over the past 10 years a variety of calcium-based materials have been examined as possible substitutes for bone in the correction of bone defects, some for use in combination with autogenous cancellous bone, others alone. Biological ceramics, derived from calcium phosphate, can be produced with varying degrees of absorbability. In some cases, like our own, it is completely non-reasorbable. The product is available either as small compact blocks or in round-shaped particles. Up to now, the particles have been mixed either with a liquid vehicle (physiological solution or blood) or with bone marrow. Such mixtures, however, were difficult to mold and tended to crumble, and this limited their use. The association of hydroxyapatite and human fibrin glue has significantly amplified the field of application. Fibrin glue is a biological adhesive system with two components. Apart from its adhesive properties, it permits immediate hemostasis and favors the repair process in damaged tissues. The system consists of freeze-dried Tissucol, a product containing coagulable human plasma proteins, freeze-dried thrombin, aprotinin and calcium chloride. Appropriately mixed, the various components solidify into a strong plasma coagulum. Lysis of the coagulum is delayed by adding aprotinin so that the fibrin reticulum formed stimulates the proliferation and growth of new fibroblasts. The fibrin glue formed in this way has a triple action: it is adhesive and hemostatic and stimulates tissue repair.

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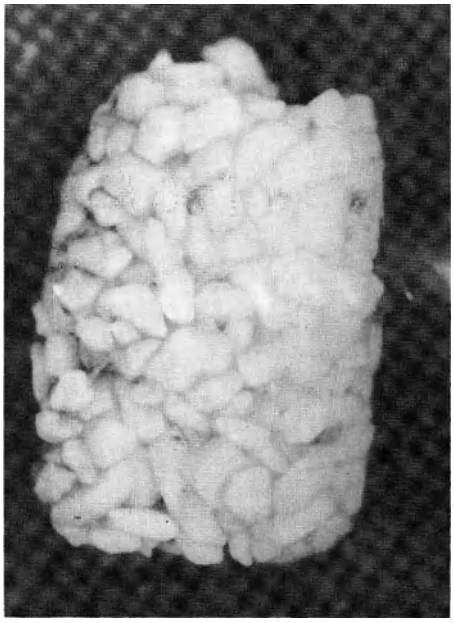

Fig. 1. Mixture of hydroxyapatite with fibrin glue

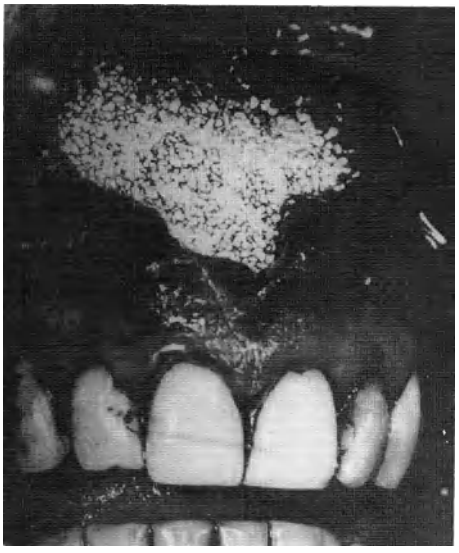

Fig. 2. Fibrin glue/hydroxyapatite delivered to the bone cavity

The slowly solidifying fibrin glue, with a low thrombin content, is mixed by Duploject with the hydroxyapatite. Then you have about 2 min to deliver the mixture (Figs. 1, 2). The combination of hydroxyapatite and fibrin glue can be used in various fields including:

1. Plastic and reconstructive surgery of the nose, to correct deformities resulting from either cleft-lip-palate or injuries
2. Surgical reconstruction of the bone, either alone or in association with an iliac bone graft, as in this case of traumatic depression of the forehead and eye
3. Surgical treatment of large cysts of the mandible and maxilla, to repair the bone wall as a support for the mucoperiosteum
4. Preprosthetic surgery, where the atrophic alveolar ridge needs to increase, as a substitute for bone grafts which are always subject to reabsorption. After tunnelling through the mucoperiosteum via two vertical incisions, the hydroxyapatite is delivered, permanently increasing the vertical dimension of the mandible
5. In periodontal surgery to fill vertical bone defects

First Case History

The treatment of the nasal deformities secondary to cleft-lip-palates is the last stage in the surgical treatment of this complex malformation. The case we present is that of a 20-year-old male with double cleft-lip-palate. He presents all the typical

sequelae of the condition, as well as widening of the nasal bone pyramid due to a short columella. The surgical principle and technique are similar to those employed in unilateral cleft lip. The alar cartilages are completely dissected by a double V incision on the lip surface. The intercartilage incisions are extended so that the columella can be lengthened and the nostrils narrowed. The first step is infiltration with local anesthetic. This is injected parallel to the nasal bridge at the cartilage incision and along the lower rim of the nasal bone.

The intercartilage incision is made in the space between the lower rim of the triangular cartilage and the upper rim of the alar cartilage. Then we mobilize the soft tissue under the dorsal skin of the nose. This operation is carried out separately on each side. Afterwards we dissect the tissues to the right using a No. 15 scalpel. The pericondium is then peeled back to the free edge of the cartilage so that the edge itself is visible. This is followed by total dissection giving access to the anterior nasal spine and then the septal cartilage is peeled back completely. The luxation method is used to reveal the alar cartilages via an incision in the vestibulum. The incision is made directly in the lower cartilage. Starting from this incision, the connective tissue above the alar cartilage can be detached with curved scissors and an elevator. In order to lengthen the columella, an incision is made in the skin to create a double V flap. Two upside down triangular flaps are then carved out. These are sutured together and moved towards the tip of the nose to form a new columella. The area of the anterior nasal spine is also bared. The nose can also be further lengthened by sliding forward the base of the septum. The scalpel is used to cut an incision as far as the nasal bridge. The front part of the cartilage is removed and replaced further forward. It is then anchored by suture stitches using nonabsorbable suture. After modeling the alar cartilage we place a suture stitch between the two medial peduncles to draw them together. This is done under direct observation. It accentuates the nose tip, narrowing and lengthening the nose. We found a new and interesting application for hydroxyapatite when reconstructing the bridge of the nose.

Our decision to mix the hydroxyapatite with fibrin glue made this application possible. The addition of the glue makes the hydroxyapatite more malleable, more cohesive and stronger so that it can be used instead of bone or other alloplastic material to support the morphological structure of the nose. A further advantage of the compound is that it can be modeled and adapted for a variety of surgical requirements, a virtue that no other biological material has offered. The mixture of hydroxyapatite and fibrin glue is delivered using a special syringe both along the median line above the septum laterally and through the intercartilage incisions. Before the glue sets it is modeled to give the bridge of the nose the desired height and profile. The hydroxyapatite is also used to support the dissected portion of the septal cartilage. It has exceptional malleability before it sets and, once set, it is strong and cohesive enough to support the bridge of the nose. Fibrin glue is used after suturing to seal the wounds and prevent any infection of the graft. The nose is then sponged, and a plaster cast is applied as an external nasal splint. Being radiopaque the graft is clearly visible in postoperative X-rays.

Second Case History

Our second case required surgery to close an oroantral and oronasal communication following the excision of a large cyst of the maxilla rising into the follicle of an impacted right upper canine. The cyst occupied the entire right half maxilla and part of the left half maxilla as far as the apex of the canine. Inadequately supported by bone, the mucosa had dehisced to create an oroantral communication. Six months after the first operation we employed our new technique for the surgical treatment of large cysts using our mixture of hydroxyapatite and fibrin glue. After cutting the rim of the communication and preparing the mucoperiosteal flaps, we reconstruct the wall and floor of the nose using contiguous flaps taken from the epithelium that covered the residual cavity after removal of the cyst. Thereafter our new technique is a three-step process:

1. We fill the lower two-thirds of the remaining bone cavity with rapid-solidification fibrin glue.
2. We inject the mixture of hydroxyapatite and fibrin glue. The hydroxyapatite is placed in the special syringe with slow solidification glue in a ratio of 1 ml glue solution to 4 g hydroxyapatite. The two ingredients are then mixed into a homogeneous compound and delivered. An elevator is used to model the hydroxyapatite and remove any excess material.
3. We apply a thin layer of fibrin glue to seal the graft and assist the adhesion of the mucous flaps over it. Finally we suture the wound. The new bone wall is clearly visible in the postoperative X-ray.

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The Management of Dentogenous Bone Cysts Using Bankbone and Fibrin Sealant (Tisseel/Tissucol)

G. WATZEK, W. LILL, and M. MATEJKA

Key words: Dentogenous cysts, bankbone, fibrin sealant

Abstract

In the present study a concept is presented for the management of dentogenous cysts using fibrin sealant and bankbone. The advantages of closed treatment over the open obturator method are discussed in greater detail as well as the histological and clinical consequences.

Introduction

From the time of Partsch [9] until very recently, cystostomy or cystectomy with subsequent treatment of the open cyst cavity has been the therapy of choice for cysts exceeding 15–20 mm in diameter. One of the reasons for this procedure is the fact that blood clot retraction occurring in the course of physiological coagulation leads to a disturbance of reossification [14]. The chief drawback of open treatment was that the postoperative wound management often took months or even years. Moreover, if in the course of cystectomy root resections had to be performed, it was necessary to shorten the root to such an extent that the tooth was likely to loosen later on. In order to find alternatives to open treatment, which is fraught with great inconvenience, numerous attempts were made to stabilize the blood clot on the one hand and to pack the cyst cavity with autologous, heterologous, or synthetic materials on the other hand. Schulte [13] proposed the use of the patients' own blood, Lehnert and Schmallenbach [5] the Kiel bone graft, Matras et al. [7] the combination of bankbone and fibrin sealant, and Dickmeisz et al. [3] fibrin sealant without bankbone. In addition, a series of synthetic materials were tested for their suitability in the packing of cyst defects [4; 11]. At our department we have used bankbone together with fibrin sealant in such cases for the past 5 years.

Method

A section is made along the gingival margin by vertical incision which has to be clearly mesial or distal of the expected bone window to avoid postoperative wound dehiscence. After detachment of the soft tissue parts the buccal bone surface is exposed. Next, buccal fenestration of the cyst cavity is performed and the cyst

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Fig. 1. The fibrin adhesion system and bankbone are the basic materials for the packing of bone defects caused by dentogenous cysts

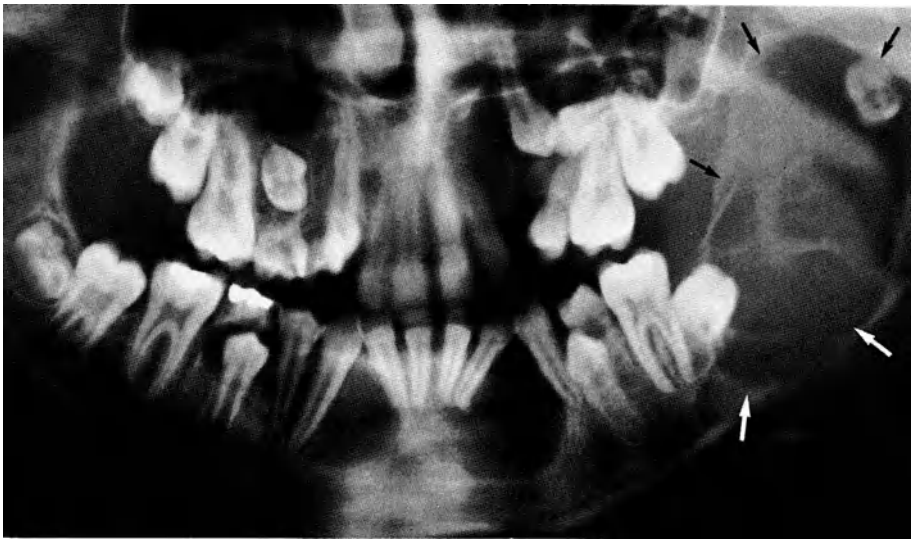
removed in toto, if possible. If, in the maxilla, there is a risk of perforation to the nasal sinus or of devitalization of adjacent teeth, it is expedient to retain portions of the cyst sac in this area. Then the mixture of bone and fibrin sealant is prepared. Depending on the size of the cyst 1–5 ml sealant is required (Fig. 1). To obtain the first component of the fibrin sealant, the lyophilized sealer protein concentrate (Tissucol) is reconstituted with the aprotinin solution, as described by the manufacturer.

The second component consists of lyophilized thrombin which is reconstituted with calcium chloride solution. The bankbone[1] (lyophilized, radioactively sterilized homologous bone) is cut into chips, mixed with the fibrin sealant, and introduced into the bone cavity, which has been rinsed with calcium chloride solution prior to packing. When filling is complete, the defect is sealed by applying a final coat of the two-component fibrin sealant and tightly sutured to protect it against salivary action.

Results

Both in follicular and in radicular cysts complete bony healing of the defects was observed (Figs. 2, 3). In several patients the inferior alveolar nerve in the mandible had to be dissected before removing the cyst and was left unprotected in the cyst cavity. In these cases osseous restoration of the mandibular canal has been observed. Even after the ablation of large cysts, especially follicular ones, complete

1 We thank Dr. Bösch from the Orthopaedic University Hospital, Vienna, for making the bankbone available.



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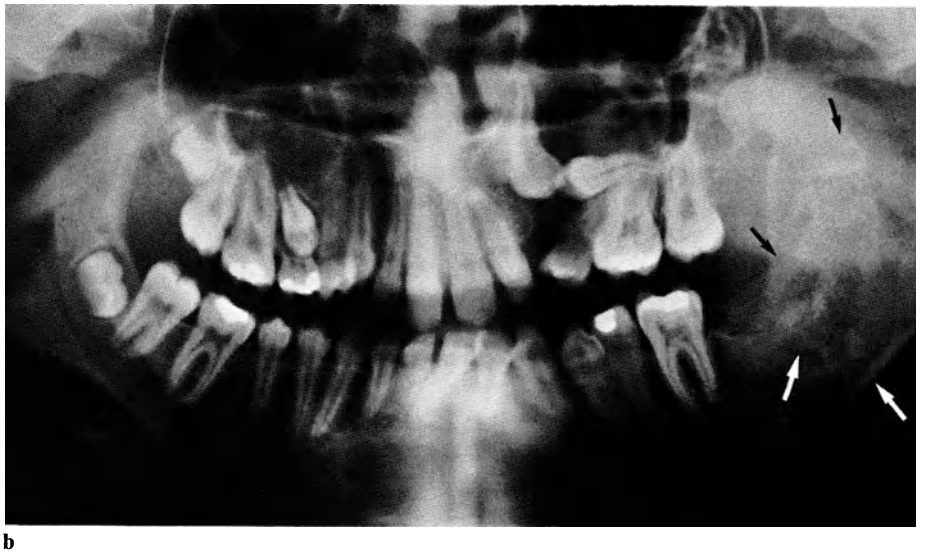
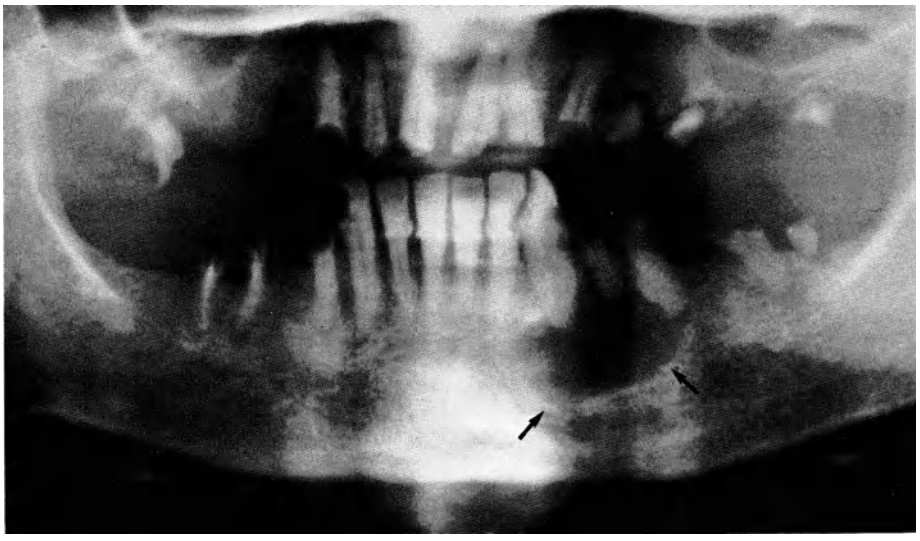


b

Fig. 2. a, b. Follicular cyst arising from 38 situated adjacently. **a** Preoperative, panoramic roentgenogram. **b** Panoramic view 37 weeks postoperatively: complete bony healing of the cyst cavity

healing has been attained within a few months by the method described. Wound dehiscence [3, 10] occurred in rare cases only, in which sequestrectomy had to be performed.



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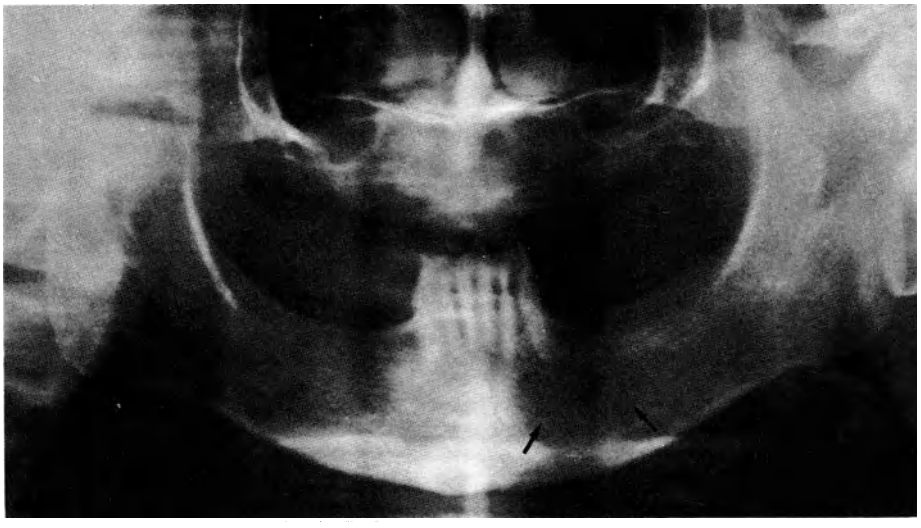

b

Fig. 3. a, b. Radicular cyst arising from radices 34 and 35. **a** Preoperative panoramic view. **b** State 27 months postoperatively: complete bony healing of the cyst cavity

Discussion

Bösch et al. [1] performed experimental investigations in rabbits to study the influence of highly concentrated fibrin on bone healing. They were able to demonstrate that the healing of autologous and heterologous bone implants was accelerated when the fibrin sealant was used. This is explained by the greater stability of the clot,

but also by earlier vascularization resulting in improved trophic conditions at the centre of the graft [2]. Moreover, it has been pointed out that the haemostatic effect of the fibrin sealant [15] prevents secondary bleeding into the cyst cavity and thus there is no secondary influx of further corpuscular elements, in particular of erythrocytes, into the cyst cavity. This may also contribute to accelerated organization into primary connective tissue in the area of a packing consisting of fibrin sealant and bone.

When, on the other hand, the fibrin sealant is applied too thickly, this has also been found to impede healing [6], since the cancellous bone chips are virtually immured and, as a consequence, ossification is postponed.

It is often argued that hepatitis may be transmitted by the fibrin adhesion system, but this risk can be excluded with a high degree of certainty [8]. The risk of infection from the buccal cavity, which no doubt was greater in the case of open treatment using an obturator, is reduced to a minimum with the method described [7]. This was also the reason why at our hospital no patient has been treated by the open method in the last 5 years. Being a homologous graft, fibrin sealant has been investigated for its immunological compatibility, but no evidence of graft rejection has been observed in any test animal [12].

In conclusion, it should be emphasised that the use of bankbone in combination with fibrin sealant in the management of large mandibular or maxillary cysts is less harassing to the patient and, moreover, causes no problems as regards the fitting and use of dentures immediately after operation. For all these considerations, the packing of extensive dentogenous bone cysts with fibrin sealant and bankbone is a highly promising method of treatment.

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The Use of Fibrin Sealant in Various Maxillosurgical Indications

H.-A. GITT and W. BETHMANN

Key words: Fibrin sealant, maxillomandibular surgery, hemostasis, wound healing

Abstract

Clinical application and clinical examinations of the fibrin sealant Tissucol (Immuno AG, Vienna) have shown the superiority of biological sealant compared with other sealing techniques. When used alone or in combination with sutures we observed an excellent hemostatic effect and acceleration of wound healing.

Introduction

We have been using various sealing techniques for years; since 1981 we have been working with the biological fibrin adhesive system. Our experiences with Tissucol (Immuno AG, Vienna) have been confirmed by references in the literature [1–11].

Material, Method and Case Reports

We applied the fibrin sealant Tissucol in 0.5-ml packs. In most cases the sealant was injected simultaneously, which has become very easy because of the Duploject system. A gelatin sponge or collagen fleece have been used as carriers. We applied Tissucol in 110 patients (72 males, 38 females) and divided them into 3 groups (Table 1).

Table 1. Total number of patients treated with fibrin sealant, sealings and postoperative bleedings observed

	Number of patients	Sealings	Postoperative bleedings
1. Anticoagulated patients	18	19	2
2. Patients with hermorrhagic diathesis	45	49	4 (2 substitutions)
3. Patients with normal coagulation	47	48	1
Total	110	116	7

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Anticoagulated Patients

18 patients had to be on anticoagulant therapy because of cardiac infarction; three patients were dialysis patients. In this group we treated 14 secondary teeth and performed 4 local excisions. The wounds were closed with Tissucol.

Patients with Hemorrhagic Diathesis

In these 45 patients a total of 21 secondary teeth and 24 deciduous teeth were extracted. Wound sealing was with Tissucol in combination with gelatin sponge or collagen fleece.

Patients with Normal Coagulation

In these 47 patients we took advantage not only of the hemostatic effect of fibrin sealant but also of its conduciveness to wound healing.

1. Prophylactic sealing of 14 extraction wounds in patients with disturbed compliance (for example, debility), where surgery was only possible with anesthesia and where treatment of postoperative bleeding would have required anesthesia again.
2. In cases dura was glued into the facial opening after operations of the maxillary sinus.
3. In seven cases of periodontal plastics we never needed dressings.
4. In six mandibular cysts we used fibrin sealant in five cases of minor cysts for complete filling of the cysts. An extensive cyst from tooth 34 to 45 was also filled with sealant (Figs. 1, 2). In addition the mandibular teeth were immobilized by a splint.
5. In five maxillary cysts we adapted a mucosal-periosteal flap using a low thrombin concentration (4 IU/ml).
6. Tissucol was applied in the surgical exposition of two impacted teeth for orthodontic indication.
7. A 15-years-old girl was injured in a riding accident; her lower vestibulum was open. In another clinic an ample mucosperiosteal flap was taken (Figs. 3, 4). In our clinic the defect was filled with fibrin sealant and extraorally managed with a compression bandage.
8. Tissucol was applied in a facial plasty in the course of a parotidectomy.
9. We used Tissucol with low thrombin concentration in combination with bone chips in a cranium plasty.
10. An extraordinary case of manually provoked papilla bleeding of a mentally ill person, which persisted over a few months, could be stopped with fibrin sealant. We were interested not only in clinical experiences but also in the efficiency of fibrin sealant regarding the adhesive or tensile strength of the sealed tissue. In a simple test with 125 measurements we calculated the strength necessary to remove a lyodura patch from the vestibular gingiva of the mandibula.

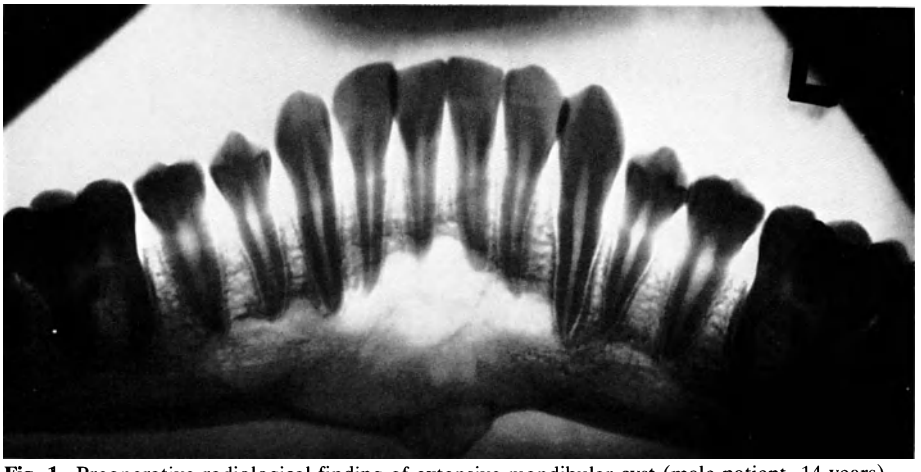

Fig. 1. Preoperative radiological finding of extensive mandibular cyst (male patient, 14 years)

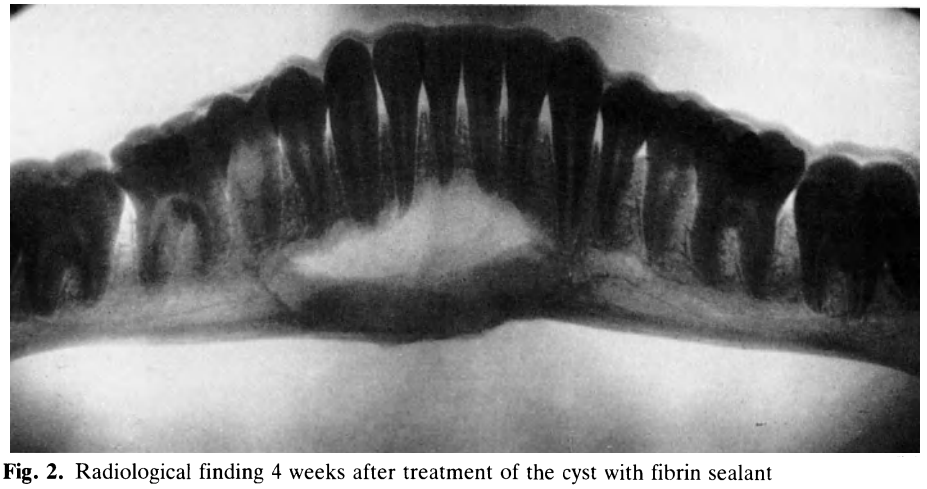

Fig. 2. Radiological finding 4 weeks after treatment of the cyst with fibrin sealant

Results

Anticoagulated Patients

In 18 applications we counted two postoperative bleedings. One postoperative bleeding of an extraction wound was managed with another sealing; one postoperatively bleeding excision wound was treated with other local measures.

Patients with Hemorrhagic Diathesis

In 45 applications we found 4 postoperative bleedings that were treated repeatedly with fibrin sealant. In two patients (hemophilia A) hospitalization and simultaneous substitution therapy were necessary.

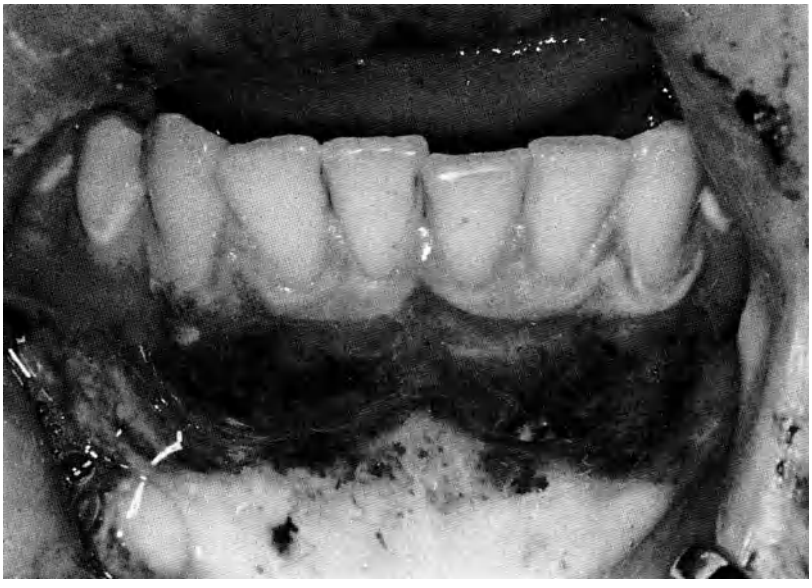

Fig. 3. Preoperative clinical finding after trauma and extensive excision *ab altera manu* of the soft parts of the lower vestibulum oris

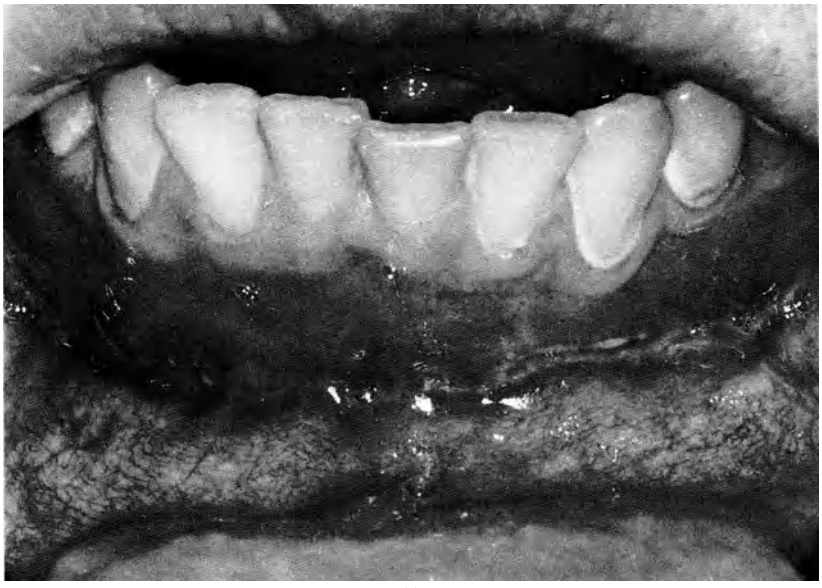

Fig. 4. Lower vestibulum oris healed without signs of irritation 8 days after treatment with fibrin sealant

Patients with Normal Blood Coagulation

1. Hemostasis of the extraction wound was safe, no postoperative bleeding
2. Wound healing without complications, no postoperative bleeding
3. Wound healing without complications, even accelerated compared with earlier interventions, no postoperative bleeding
4. Wound healing without complications. In one case of extensive mandibular cyst 4 weeks after surgery distinct bone formation could be radiologically detected (Fig.2)
5. Wound healing without complications, no postoperative bleeding
6. Wound healing without complications, no postoperative bleeding
7. Eight days after surgery we found a well-closed vestibulum without signs of irritation (Fig. 4)
8. Facial function regular
9. Regular healing of the bone chips
10. No postoperative bleeding. Clinical testing of the adhesive strength showed a mean value of 590.48 p/cm^2

Discussion

Our experience of several years of work with the fibrin adhesive system shows the broad range of application of Tissucol. In accordance with other authors [1, 2, 3, 4, 7, 10] we have observed its distinct superiority compared with other sealing techniques. We were particularly impressed by the hemostatic effect of fibrin sealant [1, 2, 3, 5, 7, 8, 9, 10].

In anticoagulated patients we never needed to interrupt this therapy, which would have been an immediate danger to the life of the patient (reinfarction) [1, 3, 7, 8, 9, 10].

One patient of this group in whom we removed a leukoplakia in the left corner of the mouth we were able to treat as an outpatient. An earlier intervention in the right corner of the mouth without Tissucol had required hospitalization and interruption of anticoagulant therapy. In most patients with hemorrhagic diathesis hemostasis was sufficient [1, 2, 3, 5, 7, 8, 9, 10]. The two postoperative bleedings in patients with hemophilia A were due to extremely low factor values and to mechanical insult. Normally we do not use protection plates in these patients, for they often provoke bleedings by mechanical irritation or pumping effects, nor do we use approximation sutures, as we sometimes observed minor bleedings from the puncture channels of the sutures. Deciduous teeth were mostly extracted in children with leukemic diseases on antineoplastic chemotherapy. We used fibrin sealant in all these interventions such as in 1, 2, 3, 7, 8, 9, and 10 with a carrier (gelatin sponge or collagen fleece) to find sufficient support in the flat alveoli.

Treatment of this group of patients with hemorrhagic diathesis is normally feasible with fibrin sealant without the risks (allergization, inhibitor formation) and costs of substitution therapy and without hospitalization. In patients with normal blood coagulation we were particularly impressed by the hemostatic effect and the accelerated and complication-free healing of the wound [2, 4, 6, 7, 8, 11].

Lyodura plastics in surgery of the maxillary sinus sealed with Tissucol always healed without complications; after application of acrylic sealants we often observed delayed wound healing. Periodontological interventions always healed without complications with retarded bone destruction [1]; after 1 year they showed smaller pockets than sutured plasties.

The acceleration of healing and the accelerated bone regeneration were particularly striking in operations of cysts (Figs. 1, 2). Our observations are thus in accordance with those of other authors [2, 7, 8]. In the traumatological case described in 7 we not only observed accelerated healing but also almost regular anatomical healing. Clinical experience (safe hemostasis and accelerated healing) as well as excellent adhesive strength and resistance emphasize the suitability of the fibrin adhesion system for numerous maxillosurgical interventions and facilitate them considerably.

Our excellent results with fibrin sealant have led to its wide spread application not only in maxillomandibular surgery, but also in organ-preserving interventions, for example, the spleen, at the Leipzig University Clinic of Surgery.

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Application of Fibrin Adhesive in Closure of Oronasal Communications with the Help of Flap Glossoplasty

H.-J. HOCHSTEIN and O. SCHENK

Key words: Residual perforation, flap of the tongue, fibrin adhesive

Abstract

The decisive advantage of flap glossoplasty in the closure of remaining perforations in the palatal area is a considerable decrease in the failure rate. In comparison to the pedicle graft with a tubed flap, the shorter stay in hospital, the smaller number of operations and duration of treatment, which is less stressing for the patient, are further advantages. Here the application of the fibrin adhesive facilitates the work of the operator and alleviates the stay at the hospital for the patient by shortening the duration of the operation. By its haemostatic properties fibrin adhesive decreases the complication rate and thus not inconsiderably contributes to the general success.

Introduction

Connections between the oral and nasal cavities may appear as a sequel of surgical interventions, as sequels of accidents, after specific inflammations and for some other reasons. The most frequent cause, however, is a congenital schistosis in this area, the primary closure of which ended with a failure. A large number of operation methods are known, with the help of which such defects may be closed by a combination of one or more interventions. Despite the full treatment of all possibilities according to the investigations of the Zurich [4] and Hamburg clinics [20] and our own examinations of patients of our clinic, repeated failure in 12%–35% of cases is to be expected. Therefore, with particularly unfavourable prerequisites, such as extended remaining clefts, several previous failures and poor conditions of blood supply, many authors [5, 6, 8, 10, 21, 22, 23, 24 and others] have decided on a covering of the defect by tubed flaps. The advantages and disadvantages of the pedicle graft are known. As a rule the closure is successful. Faced with the unsatisfactory choice of local operation methods, which have a high failure rate, or of the expanding pedicle graft with a tubed flap, which stresses the patient and has numerous other disadvantages, following Cadenat [1, 2, 3] and Guerrero-Santos [11, 12, 13], we took the recently introduced, but little used, technique of flap glossoplasty [9, 19] and further simplified and modified it. We used it with success in covering extended defects in the region of the hard palate.

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Material and Methods

Up to now we have surveyed 23 cases with flap glossoplasty. We proceeded according to the following principle. The remaining hole is circumcised; the margins of the wounds are mobilized and used for the formation of a nasal layer. If this is not possible lyophilized dura is used for the nasal layer. According to the extension and localization around the remaining hole to be covered, an area is de-epithelialized so that the flap of the tongue has a sufficiently large wound area for healing. The defect to be covered is measured and the flap to be formed is drawn onto the tongue. The taking of the flap begins as far as possible in the retrolingual region and is flapped towards the tip of the tongue. Then follows the exact closure of the wound of the donor place. The flap of the tongue is fixed above the defect to be covered by single sutures at the palate. For the prevention of postoperative bleedings, which may call into question the success of the graft, at the beginning we cover the part of the flap which is free and uncovered between the tongue and the beginning of the defect at the palate in the oral cavity with lyophilized dura in the sense of a temporary protective layer. Nowadays, we only put a layer on the free area of the wound on the flap of the tongue by means of fibrin adhesive and have abandoned the adhesion of dura. At the same time we seal up the previously sutured donor place on the tongue as well as the margin of the wound between the flap of the tongue and palate by means of tissue adhesive. For better adaptation of the flap at the palate a wound bandage according to Rosenthal [21] in the form of an acetone-celluloid plate is attached for 4 days. After 2–3 weeks the flap of the tongue healed above the defect is separated at the distal margin of the original remaining hole and the defect is finally closed. We again seal up the suture by means of the fibrin adhesive. The residual flap which is not needed for the closure of the defect undergoes a repositioning into the tongue.

Results

The average age of the 23 patients operated on according to the above-described technique was about 35 years. The youngest was 7, the eldest 61 years. For the final covering of the defect by means of the tongue flapping as a rule two operative sessions were necessary. Only in four patients did we have to perform a third and in

Table 1. Comparison of results for closure of palatal defects by means of tubed flapping and flap glossoplasty

	Tube flap	Tongue flap
Number of patients	20	23
Age in years	21	35
(minimum – maximum)	(8–42)	(7–61)
Stay in hospital in weeks	30	6.6
(minimum – maximum)	(16–61)	(4.2–12)
Number of operations	7	2.3
(minimum – maximum)	(4–11)	(2–4)

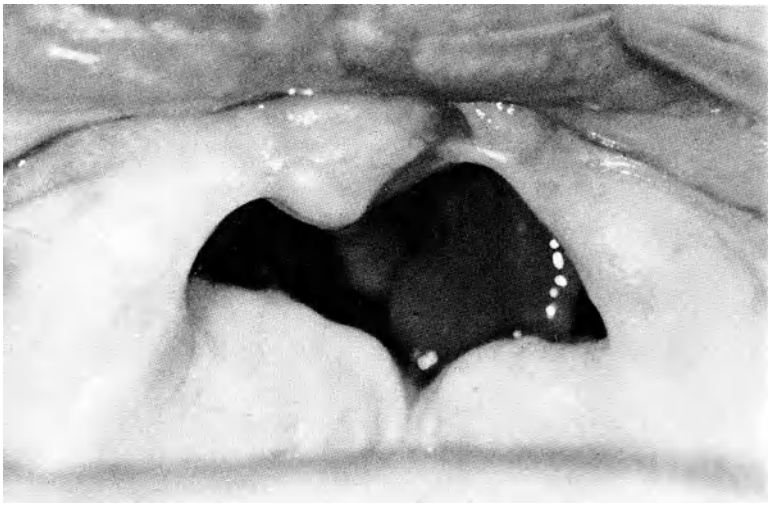

Fig. 1. Large, repeatedly operated on remaining cleft in an anodont patient

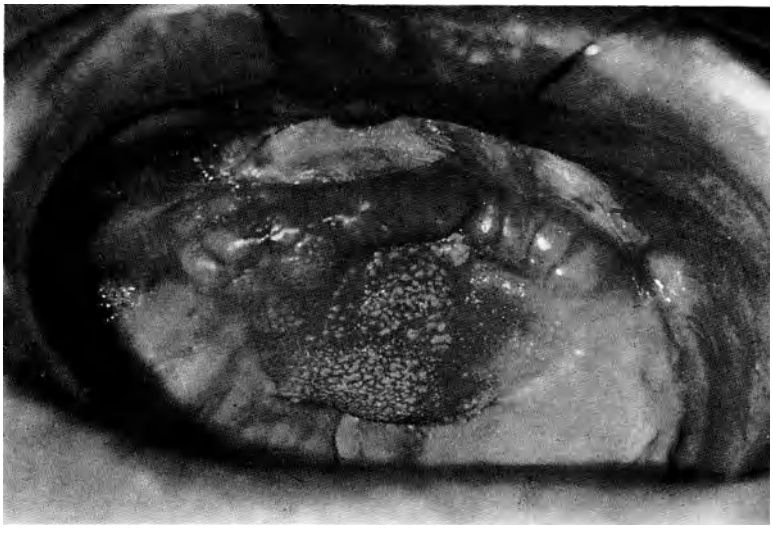

Fig. 2. Condition after operative closure with tongue flapping and plastic operation of the vestibulum of the mouth with a free compound flap graft

one case a fourth corrective surgical intervention. The average stay in the clinic was 6.6 weeks.

Two clinical instances demonstrate our method of flap glossoplasty using fibrin adhesive. The first case (Figs. 1, 2) was a patient who for 15 years carried a tubed flap on the arm, having decided not to have an implantation into the mouth. With the functionally fully insufficient prosthesis he was considerably impaired when eating and speaking. After successfully performed tongue flapping we then carried out a plastic operation of the vestibulum of the mouth with help of a freely

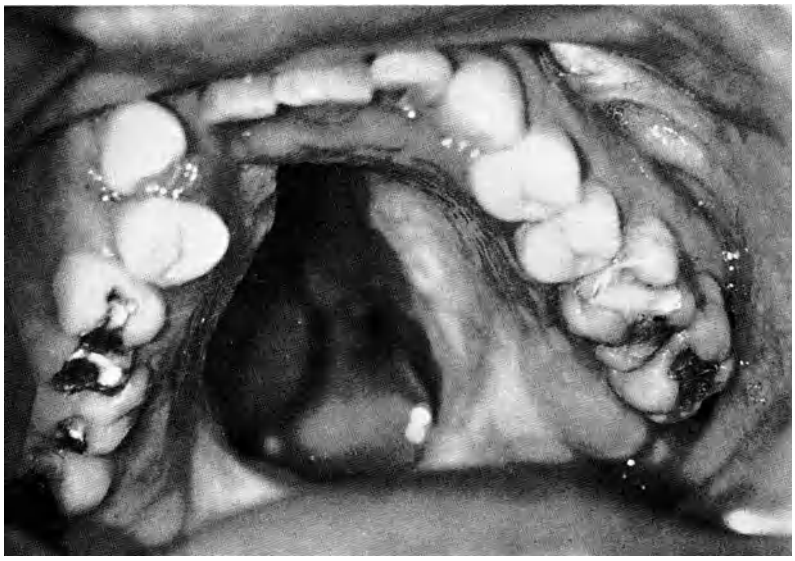

Fig. 3. Large remaining cleft in juvenile patients

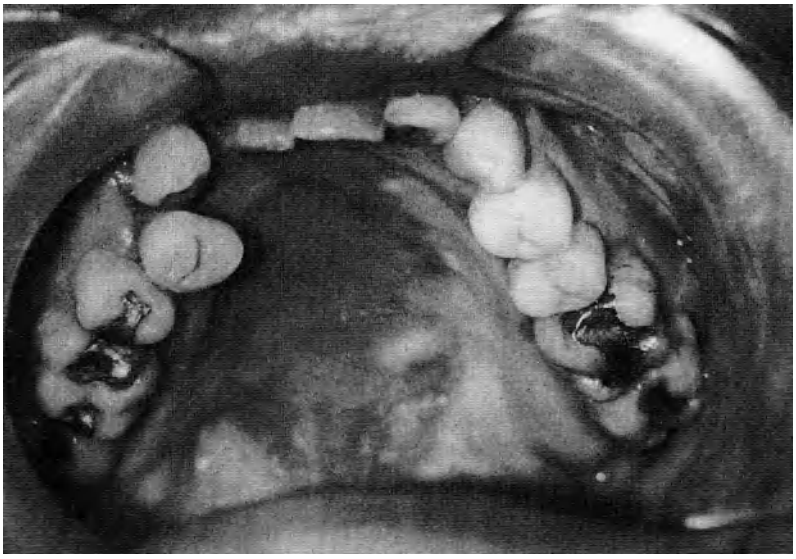

Fig. 4. Condition after operative closure with tongue flapping. The nasal layer was partly formed by lyophilized dura

transplanted compound flap. The fixation of this graft was also carried out by means of fibrin adhesive. The second case (Figs. 3, 4) was a young patient with a remaining cleft which had been repeatedly operated on without success. On account of the size of the remaining hole, for the complete formation of the nasal layer a temporary implantation of lyophilized dura had to be performed.

Discussion

The advantages of the operative closure of remaining defects in the palatal region in comparison to a solely conservative prosthetic treatment are unequivocal. Among others, they consist in significant improvement of speech, a better prerequisite of the prosthetic care, removal of chronic irritative appearances in the nasal space by the entry of the food from the mouth into the nose, improved environmental contacts and thus a better psychic situation of the patient. Though Waßmund [25] has already referred to the covering of the defect with the help of tongue flaps, up to now the technique is not undisputed. When it is used, many authors [2, 11, 12, 13] at least recommend great – in our opinion unnecessary – expenditure for securing the result of the operation. To this belong the additional suturing of the tongue on the lower and upper lip, the so-called double or triple fixation according to Guerrero-Santos [13] and the intermaxillary tying which Dumbach and Steinhäuser [7] recently recommended as definitely necessary. For more than 10 years we have used tongue flapping and in no case have we performed double or triple fixation and intermaxillary tying [14, 15, 16, 17, 18]. Only with the help of a capeline bandage and a transnasally lying nose sound through which the patient is nourished for 10 days do we try to restrict the oral aperture and thus bring about relative immobilization. Always then, when the patient becomes nervous, wants to speak, or tries to open the mouth, the danger is that the graft will be injured. A postoperative haemorrhage is the most frequent cause for this and for further manipulations by the physician. This haemorrhage, which, however, rarely occurs, may take place from the donor area of the tongue flap from the tongue. As a rule it appears from the part of the flap which is free and uncovered between the end of the tongue and the insertion of the defect at the palate within the oral cavity. Particularly in large defects the flap must be formed fairly strongly in order to guarantee the blood supply at the tip of the flap. Ligations do not last well in this tissue. Use of purse-string ligatures has the great danger that vessels which are important for the nutrition of the flap are also ligated. Therefore, we at first covered this free wound area with lyophilized dura in the sense of a temporary protective layer. The dura was bilaterally sutured at the lateral margin of the tongue. Since tissue adhesives have been at our disposal, we have pasted the lyophilized dura. As to the acrylate adhesives we then had to remove the adhesive layer that the patient, when after several days the solution takes place, does not aspirate or when other reactive appearances develop in the pharyngeal space. This does not take place in the fibrin adhesives. By sealing up the free muscular tissue as well as the suture areas the danger of postoperative bleeding diminishes, which in any case we have not been able to observe since we have used this combined suture and adhesive technique. Certainly, the adhesive also causes a fixation effect not evident to us, which contributes to the success of the plastic operation.

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The Use of Fibrin Adhesive in Dental Practice

G. SCHARGUS

Key words: Cysts, dental practice, mucosa, oral cavity, palatinal gum, postoperative bleeding

Abstract

In dental practice and especially in oral surgery, the fibrin adhesive has proved its great usefulness. In combined use with collagen, vigorous abnormal bleeding can be stopped. Cystic cavities and alveoli can be filled. Better adaptation of mucosa flaps as used for sealing oral–antral connections or in vestibular plasty or in the palatinal region can be achieved, helping to make oral surgery more convenient and improving its methods.

Introduction

Impairment of wound healing often follows small operations in the oral cavity. Early and late complications may occur. Only abnormal bleeding after tooth extractions is found in the immediate postoperative period. It is caused by a reciprocal reaction to the use of vasoconstricting agent added to most local anesthetics. Late complications usually are caused by infections following dehiscence of the suture or by the dissolution of the hematoma in the osseous cavity or a dry socket. Having no direct intraoperative bacterial inoculation all the hazards listed are provoked by vigorous and lacking bleeding or by prematural fibrinolysis of the formed hematoma. Even though there are quite a number of therapies for these complications, at times the procedures are very tedious and difficult. Until recently we had no possibility of prophylactic management of the cause of impaired healing by prompt hemostasis, stabilizing the hematoma and prolonging the adhesion of the wound edges for better resistance against the fibrinolytic activity of the saliva. To achieve these goals rapid hemostasis and wound adhesion are required, with the exception of therapy for the dry socket.

A multitude of authors had worked on the problem of fibrin adhesive, until in 1970 Matras was able to introduce a practical method. Based on this fundamental research, Immuno developed the fibrin adhesive Tissucol that meets all the demands. This product has been used successfully since 1979 to avoid or treat wound healing problems in dental surgery, including in the dental practice.

Methods and Results (Figs. 1–10)

We shall discuss the use of Tissucol in the context of its various indications.

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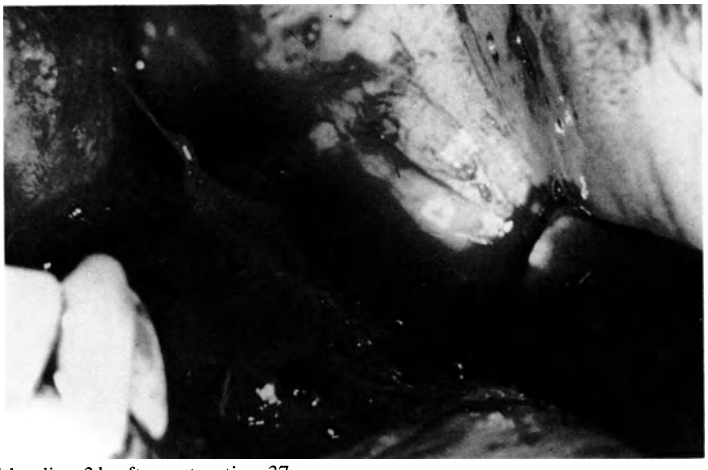

Fig. 1. Post-operative bleeding 3 h after extraction 37

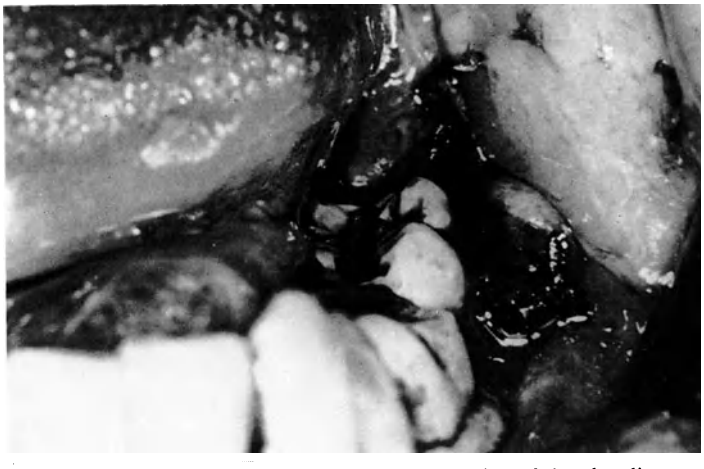

Fig. 2. Wound after closure with a collagen and fibrin seal inlay and suturing of the alveoli

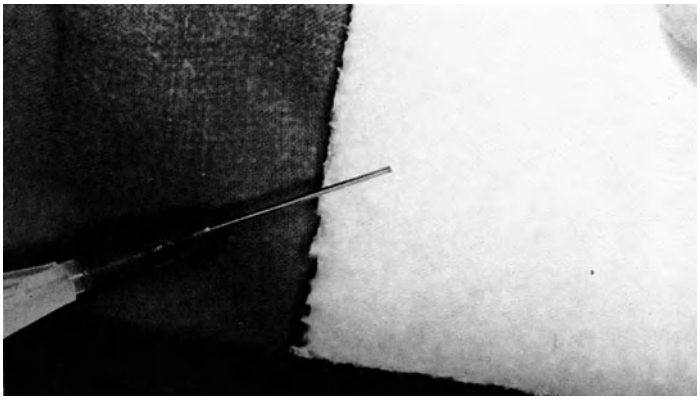

Fig. 3. Soaking of the collagen foam with fibrin sealant (Tissucol)

Fig. 5. Application of collagen-fibrin sealant-inlay into the cyst cavity

Fig. 4. Empty cyst cavity after extirpation of the cyst

Fig. 6. The collagen soaked with blood is covered with fibrin sealant

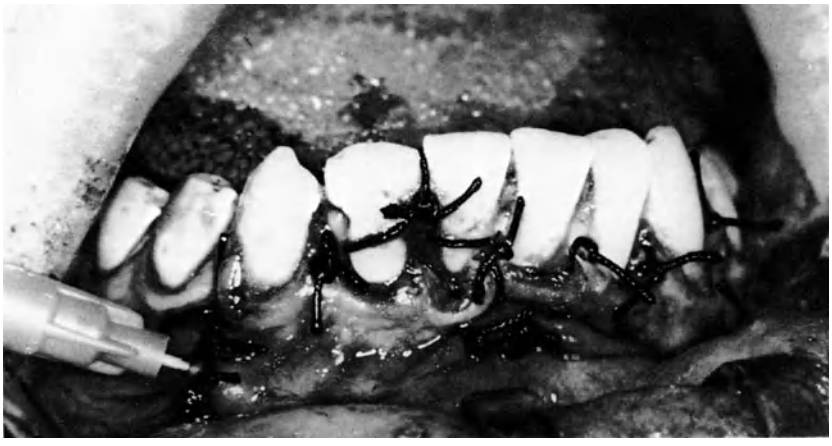

Fig. 7. Subjacent injection of the mucoperiosteum with Tissucol

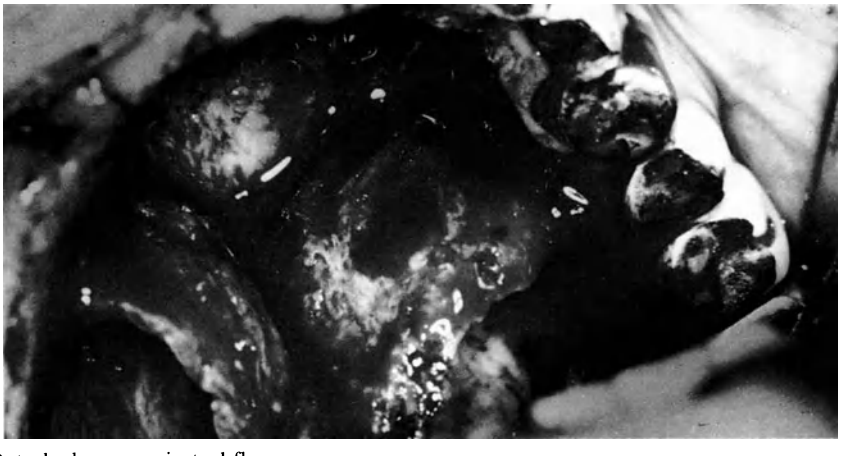

Fig. 8. Detached mucoperiosteal flap

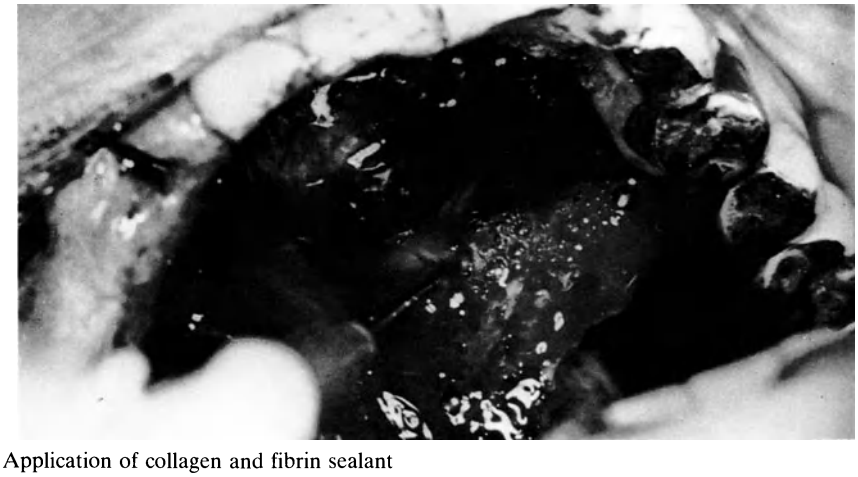

Fig. 9. Application of collagen and fibrin sealant

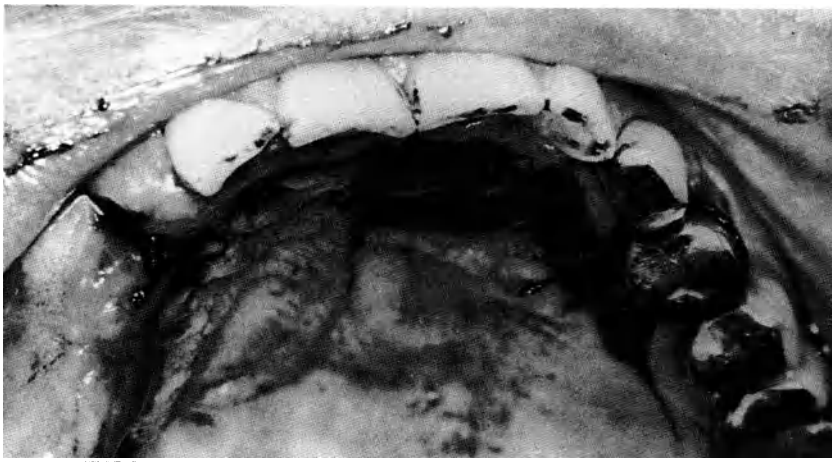

Fig. 10. Adapted mucoperiosteal flap

Abnormal Postoperative Bleeding

After small surgical interventions in the oral cavity massive abnormal and even life-threatening postoperative bleeding may occur. Following immediate removal of all fresh and clotted blood and application of a digital or bite plug on the wound, an exact history of coagulation disorders, vascular problems, hypertension, leukemia, liver diseases, and intestinal malabsorption must be taken. Bleeding from a major vessel can only be found in regions directly supplied by the palatine and lingual arteries and the mandibular artery in the bone. Abnormal bleedings not caused by coagulation disorders or internal diseases derive from minor vessels of the soft and osseous tissue. The origin often cannot be found when bleeding is vigorous. Hemorrhage occurs as a reaction to the addition of vascular constricting agents to local anesthetics. After the effect of these agents has ceased, small vessels are reopened and the existing clots can be drained, resulting in abnormal bleeding. Experience of such an incident is an unforgettable experience for a young assistant doctor. Even when one uses all known local mechanical hemostatic methods, the patient may still keep on bleeding vigorously, becoming more and more pallid and nervous. Plugging the wound mechanically or by biting shows no result. Even mattress sutures of the gingival tissue normally bring about only short hemostasis. Powdered or liquid hemostatics will be drained out of the wound by continuously vigorous blood flow. Installation of gelatin, collagen, fibrin sponges, or Sorbaceel into the alveoli brings only insufficient relief of the bleeding. In cases of such vigorous abnormal bleeding we now can routinely insert collagen sponge soaked with Tissucol and suture the wound typically. It is advisable to use a piece of collagen large enough to fill the alveoli, and often a total commercially soldered plate of collagen folded after soaking each layer is necessary. The plug has to be fixed in the wound until the suture is completed and final sealing of the wound surface with fibrin adhesive is required. It is indispensable to check on the hemoglobin and the hematocrit, as hemoglobin levels of $< 6\,g/100\,ml$ after abnormal free bleeding require immediate transfusion.

Cysts with Collagen and Fibrin Adhesive

The treatment of dentogenic cysts by cystectomy (PARTSCH II) was improved by the method of Schulte, who filled the osseous cavity with blood, penicillin, and a gelatin sponge (Gelastypt). To puncture a vein often is rather difficult, especially for a dentist. Fortunately this task is not often necessary as bleeding in the osseous cavity is plentiful. The problem we have to face is to stabilize the clot in the cystic cavity and to accelerate the osseous regeneration. After extracting the cyst wall we fill the osseous cavity with collagen and Tissucol using the same method we described previously. We suture the mucoperiosteal flap and glue it to the adherent bone using light pressure for 3 min. The hemostatic character of the fibrin adhesive prevents further hemorrhage and dislocation of the flap.

Oral-antral connections

A connection may inadvertently be established between the oral cavity and the maxillary sinus after extraction of teeth of which attical inflammation has destroyed the socket bordering the maxillary sinus or after removing the root of a molar or premolar. In the case of a noninflamed maxillary sinus this connection immediately has to be sealed to avoid sinusitis. In the case of a preexistent acute maxillary sinusitis, immediate closure would be contraindicated because of the high risk of impaired healing due to the inflammation with loss of valuable soft tissue. In such a case one should first use antibiotic therapy to convert the acute inflammation into a chronic process. Thereafter sinus operation using a consultive Caldwell-Luc-method with closure of the connection as described by Rehrmann is necessary. The weak point in this plasty procedure is the approximative reaching of the flap neighboring the teeth. The intradental mucoperiosteum is often injured by the extraction, resulting in the necessity of adapting the flap to the tooth directly. If no stable clot can be achieved underlying this region, residual perforation persists which is extraordinarily difficult to manage. Since 1980 Tissucol in combination with collagen has been a very valuable adjuvant to manage these problems. We can achieve a stable filling of the alveoli and a complete sealing of the flap by application of the adhesive to the wound edges bordering the teeth. In 1984 Gattinger introduced a method closing small oral-antral connections by inserting only a small collagen plug into the alveoli. We can recommend this method, too, and use it routinely in sinusitis; it provides the patient with a good chance of avoiding sinus operation and hospitalization.

Fixation of the Palatinal Gum to the Maxilla

To remove retained canine teeth in the palatinal region the gum has to be mobilized at least up to the premolars. To avoid bleeding and formation of hematomas between the mucoperiosteal flap and bone, a palatinal plate has to be manufactured by the technician or an acrylic wire splint made after the operation. In treating more and more allergic patients, we are often confronted with the problem of palatinal

hemorrhage and hematomas. In these cases the fibrin adhesive is of great value. After filling the alveoli and operation cavity with collagen and Tissucol, the adhesive is installed under the mucoperiosteal flap and the gum is pressed to the bone for 3–5 min. Using this method we have had entirely primary wound healing without any complications. Patients without a palatinal plate only have to avoid hard food for 3–5 days.

Adaption of the Mucosa After Vestibulum Plasty

The main problem after vestibulum plasty is the fixation of the mucosa in the vestibular sulcus, as reflected in the multitude of operative methods used today. To avoid application of surgical dressings fixed by circumferential maxillofacial wiring or mandibular fixation by zygomatic fixation or peralveolar fixation with perforation of the maxillary sinus, transalveolar screwing suture of the mucosa to the periosteal tissue is necessary. As suturing often is not sufficient, the fibrin adhesive can be very helpful. We apply Tissucol to the undermined mucosa and adapt it by pressing with a muslin dressing on the sulcus for 5 min. After 14 days the edema has faded and the result can be evaluated.

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Wound Management in Oral Surgery Using the Fibrin Adhesion System (Tissucol/Tisseel)

F. WEPNER

Key words: Oral surgery, local hemostasis, fibrin adhesion

Abstract

At the General Hospital in Linz, a fibrinogen concentrate made from human plasma (Tissucol) has been used to seal a total of 1144 wounds in 434 patients with bleeding disorders in the course of 8 years (April 1977 to February 1985).

In 293 anticoagulated patients application of the sealant was indicated for serial extractions, major oral surgery or acute inflammations. In 129 patients with bleeding disorders due to impaired thrombocyte function or defective coagulation 302 wounds were sealed. In anticoagulated patients and in patients with thrombocytopathies excellent results were obtained. In these cases withdrawal of anticoagulant medication or replacement therapy was avoided. In patients with hemophilia it proved necessary to administer factor VIII and IX concentrates, although in reduced quantities.

Introduction

Since *Matras*, [4], in 1972, reported on the nonsutured union of severed nerves using concentrated human fibrinogen, the fibrin adhesion system has gained more and more importance in operative medicine.

At the Department of Maxillofacial Surgery of the General Hospital in Linz the physiological tissue sealant Tissucol has been used since 1977, predominantly in oral surgery with a view to enhancing local hemostasis after tooth extractions in patients with bleeding disorders [10].

Material and Methods

For wound sealing a two-component fibrin adhesion system (Tissucol, Immuno AG, Vienna), which is available either deep-frozen or lyophilized, was used. The conversion of the fibrinogen component into fibrin, i.e., clotting of the sealant, is initiated by adding a solution of aprotinin, calcium chloride, and thrombin; the necessary constituents are contained in the kit accompanying the sealant. For most dentoalveolar applications fibrinogen quantities of 0.5 ml are sufficient. As we use the high thrombin concentration of 500 NIH/ml, the fibrinogen solution is clotted within seconds.

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The two-sealant components are applied separately to the site of sealing. Unlike the premixing technique which has proved useful in other fields of surgery, this method has the advantage that the site of application can be coated with the sealant components several times and, thus, minor leaks between the fibrin clot and the socket are instantly repaired.

To seal wounds left after tooth extractions, we proceed as follows: After extraction of the tooth, the socket is suctioned to keep the site as dry as possible. A piece of collagen fleece (Pentapharm AG, Basle; Disperga, Vienna; or Hormon Chemie, Munich) is cut to an adequate size and shape, abundantly soaked with fibrinogen, and introduced into the alveolus. The thrombin solution is dropped into the socket shortly before and after application of the fibrinogen component. To ensure firm adhesion of the solidifying fibrin clot to the gingival tissue, the wound edges are compressed with a moist sponge for 1–2 min until the seal has strengthened. For continued wound edge approximation, a chromic catgut suture is placed. The mechanical compression of the wound provided in this way is considered to offset the tissue trauma caused by the suture. Finally, the wound area, including the puncture channels of the suture, is sealed again toward the buccal cavity.

Patients

As mentioned initially, a total of 1144 wounds in 434 patients have been sealed at our hospital between April 1977 and February 1985. Depending on the different indications for applying the sealant, we distinguish three groups of patients (Table 1).

Group 1 (Table 2) included 293 patients receiving anticoagulants in whom wound sealing was performed following serial extractions, oral surgery, or acute inflammations. In these 293 patients 828 wounds were sealed, including 648 tooth extractions and 180 minor surgical procedures (apicectomies, removal of roots or impacted teeth) during 342 treatment periods. Normally, 0.2–0.35 ml fibrin sealant was used per site of sealing.

Table 1. Indications for the application of fibrin sealant

	Patients	Number of treatment periods	Sealant applications
Total	434	506	1144
Group 1 anticoagulant therapy	293	342	828
Group 2: bleeding disorders	129	152	302
Group 3: normal coagulation	12	12	14

Table 2. Group 1: patients receiving anticoagulants

	Patients	Treatment periods	Wounds	Fibrin sealant/tooth (ml)
Total	293	342	828	
Surgical procedures (IT, SR, RA)	135	156	180	0.35
Extractions	158	186	648	0.2

IT, removal of an impacted tooth; SR, surgical removal of a tooth; RA, root amputation

In group 2 (Table 3), consisting of 129 patients with bleeding disorders caused by thrombocytopathies or coagulopathies, 302 wound sealings were performed in 152 treatment periods. In this group were 48 patients with hemophilia A and 6 with Christmas disease in whom altogether 60 sealings were performed. Ten out of 30 thrombocytopenia patients were severe cases (platelet counts less than 20 000/mm^3), 9 patients had platelet counts between 40 000 and 60 000/mm^3, and 11 patients, in addition to thrombocytopenia, had disorders of thrombocyte function. In 28 patients, the thrombocyte function alone was impaired; 2 patients had type I thrombasthenia, their bleeding time being 30 min.

Table 3. Group 2: patients with bleeding disorders (I)

	Patients	Treatment periods	Wounds	Fibrin sealant/tooth (ml)
Total (Tables 3, 4)	129	152	302	$\frac{I}{n}$
Hemophilia A (in parentheses: SR)	48	54	82 (15)	0.30
Hemophilia B	6	6	9	0.50
Hemophilia with inhibitor	3	3	6	0.20
Von Willebrand's disease (in parentheses: SR, IT, RA)	14	15	22 (10)	0.30
Thrombocytopenia (in parentheses: SR)	30	36	76 (7)	0.25
Thrombocytopathies	28	29	93 (14)	0.20

Table 4. Group 2: patients with bleeding disorders (II)

	Patients	Treatment periods	Wounds	Fibrin sealant/tooth (ml)
Total	129	152	302	$\frac{I}{n}$
Impaired thrombocyte function due to aspirin (in parentheses: IT and SR)	3	3	5 (3)	0.15
Carriers of hemophilia A (in parentheses: IT and SR)	2	3	6 (2)	0.20
Hemodialysis (in parentheses: SR)	2	2	2 (1)	0.40
Polycythemia	1	1	1	0.40

In eight cases (Table 4), wounds were sealed in patients with bleeding tendencies in whom normally conservative wound management (with stypic agents, such as fibrin sponges, gelatin sponges, surgical sutures) should have been sufficient to provide local hemostasis. In these patients, the use of the sealant was indicated, as conservative measures had failed to stop bleeding following tooth extractions mostly performed at other clinics. In this group were two patients with transient impairment of the thrombocyte function due to ingestion of aspirin, three carriers of hemophilia A, two patients undergoing hemodialysis, and one patient with polycythemia.

The patients in *group 3* (Table 5) had no coagulation disorders. The fibrin adhesion system was used for closing three oroantral fistulas, for the fixation of one full-thickness skin graft and one split-thickness skin graft, for hemostasis following the palliative removal of a maxillary carcinoma, and for the fixation and sealing of a

Table 5. Group 3: patients with normal coagulation

	Patients	Operation sites	Fibrin sealant/site (ml)
Total	12	14	$\frac{I}{n}$
Closure of oroantral fistulas	3	3	0.5
Full-thickness skin graft	1	1	0.3
Sealing of parotid duct	1	1	0.3
Split-thickness skin grafts	1	3	0.5
Palliative removal of maxillary carcinoma	1	1	0.5
Severe bleeding after tooth extraction	3	3	0.4
Alveolitis	1	1	0.3
Root transfixation	1	1	0.3

severed parotid duct. In one patient with extremely painful, intractable alveolitis, the socket was sealed, although there was no bleeding.

In three patients with case histories of repeated postoperative hemorrhages, the fibrin sealant was applied to arrest severe bleeding after tooth extractions had been performed at other clinics; laboratory evidence showed that coagulation was normal in all three cases.

Results

Without exception, there was primary wound healing after fibrin sealing, though some of the extractions and sealings had to be carried out in the acute stages of apical infection. Alveolitis (postextraction dolor), which is observed in 1% of all cases after tooth extractions, occurred in none of our patients [5]. This may be attributable to improved wound healing due to accelerated proliferation of capillaries and formation of granulation tissue [7, 1], but also to the fact that in comparison with the natural blood clot the fibrin seal is less susceptible to infection [8].

In 42 out of 434 patients, in whom a total of 1144 wounds had been sealed, there were altogether 52 hemorrhages from sealed extraction wounds (Table 6); 63 reapplications of fibrin sealant were necessary for the ultimate control of bleeding in these cases.

Excellent results were obtained in patients with a bleeding tendency caused by thrombocytopathies or anticoagulant therapy. In these patients, replacement therapy or the withdrawal of anticoagulant medication was avoided. In comparison

Table 6. Hemorrhages from sealed extraction wounds

	Patients	Wounds	Hemorrhages from sealed extraction wounds	Reapplications of sealant
Total	434	1144	42 patients	63
Anticoagulant therapy Two or more teeth/ treatment period	237	772	15 patients	23
One tooth/ treatment period	56	56	6 patients	6
Hemophilia A	48	82	14 patients	21
Hemophilia B	6	4	2 patients	2
Von Willebrand's disease	14	15	2 patients	2
Thrombocytopenia and impaired thrombocyte function (myelofibrosis)	50	168	3 patients	7

with the withdrawal of anticoagulants, fibrin adhesion has the advantage that it carries no risk of thromboembolism and furthermore presents less mental stress to the patients than discontinuing a therapy that is understood to be essential [6].

It was more difficult to achieve hemostasis in 54 patients with hemophilia, of whom 16 had postoperative hemorrhages. These were cases of slight, but persistent oozing which started between the fourth and the seventh postoperative day. Gastpar [2, 3] attributed these postoperative hemorrhages to increased fibrinolytic action in the oral cavity and to the fact that in patients with hemophilia the blood clot is of inferior quality, even if an adequate amount of the deficient factor is replaced. Once the fibrin clot, by which vessels are sealed externally, has been lysed, the intravascular fibrin clot in hemophiliacs lacks the strength to resist the pressure of the bloodstream. Moreover, lack of vascular contraction, which is essential for hemostasis but missing in the region of the alveolar bone [9], may lead to hemorrhage from the damaged alveolar vessels, even several days after the intervention.

Though initially we sought to avoid prophylactic replacement with coagulation factor concentrates in patients with hemophilia, in May 1979 we started to administer a single dose of 500 units Kryobulin (7–15 U/kg bodyweight) prior to extraction in patients with mild hemophilia A. In patients with severe hemophilia A, 1000 U Kryobulin is administered before extraction and another 500 U on the same evening. In cases of resealing, 500 U Kryobulin is given to the patient before sealing and another 500 U after 12 h.

Discussion

In conclusion it should be emphasized that the physiologic tissue sealant Tissucol has proved to be a valuable adjunct for attaining hemostasis after tooth extractions. Especially the replacement with coagulation factors can be considerably reduced. Though a minimal risk of hepatitis transmission ought to be considered, a number of advantages, i.e., excellent tissue tolerance and complete absorption, speak in favor of the use of the physiologic tissue sealant.

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Complications in Hemophilic Patients Under Conditions of Fibrin Sealing

G. GRIMM and R. NIEKISCH

Key words: Hemophilia center; inhibitor hemophilia; FEIBAtherapy

Abstract

After describing the organization of controlling patients with hemophilia at a maxillofacial clinic the leading role of fibrin sealing in the supply of intraoral wounds in patients suffering from hemorrhagic diseases is emphasized. In 5% of all operative interventions an additional factor-VIII substitution could not be avoided. In one of these patients inhibitor hemophilia following tooth extraction developed. Extensive hematomas obstructing breathing made a tracheotomy necessary from vital indication. Life-saving therapy was possible by the prothrombin complex preparation FEIBA Immuno.

Introduction

The hemophilia center at our clinic is now involved with 112 patients. As illustrated in Table 1, hemophilia A is most frequently observed, well in front of other hemorrhagic diatheses. With this form of organizational care for hemophiliacs, our aim is to provide intensive stomatological treatment, with every possibility for preventing dental disorders. Even tooth extraction should be carefully planned to prevent inflammatory processes. This presumes that the patients are regularly

Table 1. The 112 Patients managed by the hemophilia center

	Degree of clinical severity		
	Severe	Medium	Mild
Hemophilia A	22	32	16
Hemophilia B	1	6	10
Willebrand-Jürgenssyndrome	3	8	2
Inhibitorhemophilia	1	1	1
Thrombocytopenia	–	1	4
Other hemorrhagic diatheses	–	2	2
Total	27	50	35

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checked at 3- to 6-month intervals and that – in close cooperation with the physician and pediatrician – up-to-date coagulative physiological parameters are available (Niekisch 1985, Schulz 1973).

By the introduction of sealing the treatment of intraoral wounds was made considerably easier and managed in the outpatient department. Due to this fact the highly expensive substitution therapy of the missing coagulation-factor was reduced. Fibrin sealing is now the predominant method for managing intraoral wounds, particularly extraction wounds. This biological wound sealant is reliable in hemostasis, as well as resorbable and elastic. Above all it promotes the healing of wounds and the regeneration of bones. As to these two characteristics it is far better than all other sealing methods tested so far (Matras et al. 1978; Niekisch 1980, etc.).

Nevertheless, Tables 2 and 3 show that we have to cope with the problem of postoperative hemorrhage. In 20% of our patients hemorrhage occurred after

Table 2. Results of fibrin sealing of oral wounds in different hemorrhagic diatheses

	Tissucol		
	Number of patients	Postoperative hemorrhage	Necessity of substitution
Hemophilia A	21	7	4
Hemophilia B	3	–	–
Willebrand-Jürgenssyndrome	10	2	–
Inhibitorhemophilia	3	1	1
Thrombocytopenia	5	1	–
Anticoagulant patients	25	3	–
Other hemorrhagic diatheses	6	1	–
Total patients	72	15	5
Relative frequency	100%	20.8%	6.9%

Table 3. Indication for fibrin sealing in hemorrhagic diatheses

	Tissucol		
	Number of cases	Postoperative hemorrhage	Necessity of substitution
Tooth extraction	108	14	5
Operative removal of tooth	10	1	1
Apicectomy	3	–	–
Bleeding of gingiva	5	2	–
Total operations	126	17	6
Relative frequency	100%	13.4%	4.8%

wound sealing with fibrin sealant (Tissucol). Two-thirds of these cases were successfully controlled by a second sealing.

In five patients, i.e., 7%, however, substitution therapy could not be avoided. As Table 2 also shows, these patients suffered from hemophilia A. Analyzing these patients according to the nature of the surgical operation, we see that of all the operations postoperative bleeding occurred in only 13.4%. In only 5% substitution therapy have to be applied. Tooth extraction was the predominant indication. Both surveys illustrate that the majority of cases of hemorrhage can be controlled by fibrin sealing.

But in cases which require substitution therapy there is still the problem of reactions on the transfusion of concentrated coagulative factors in the form of coagulation inhibitors. We are confronted with this problem in approximately 5%–20% of all cases after repeated substitution therapy. Fatal complications may result from neglecting the problem.

Though bleeding of an extraction wound may be prevented by using human fibrin sealant; the insufficient coagulation capacity in cases of inhibitor hemophilia may result in extensive hemotomas in the adjoining soft tissues associated with fatal obstruction of the airway. We have to consider such a course and to initiate early preventive treatment. Significant therapeutic and preventive consequences are discussed in a dramatic representation of a case of inhibitor hemophilia (Schulz 1984).

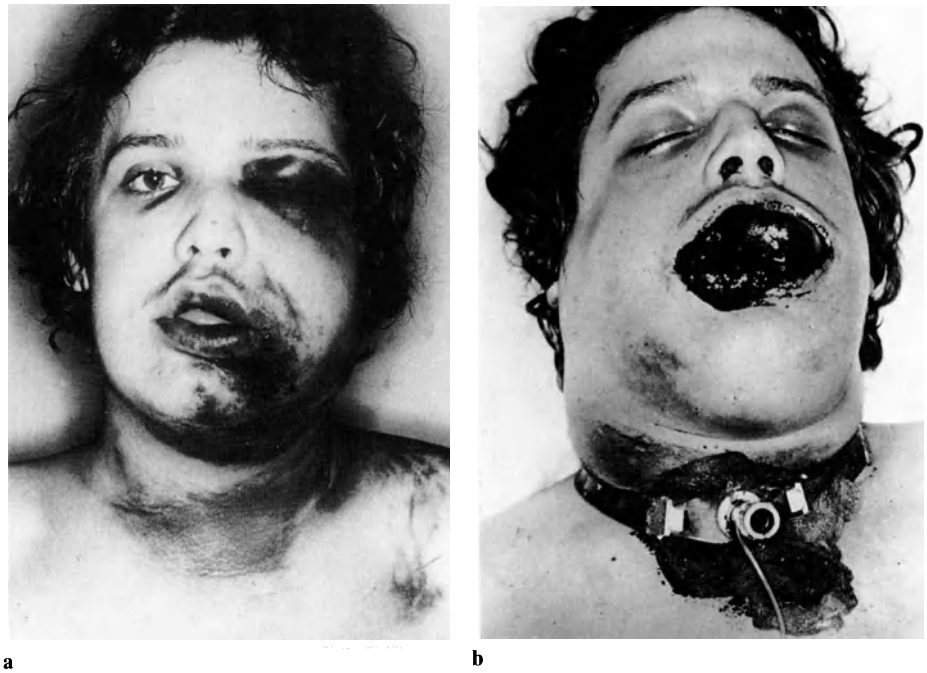
Case Report

A 19-year-old male patient with a known history of hemophilia A had – following tooth extractions 2 years previously – experienced a substitution by cryoprecipitates (concentrated antihemophilic factor A) twice.

The hemotomas following the second extraction were within tolerable limits (Fig. 1a), whereas highly extensive, massive hemotomas developed when 16 days later the extraction of two molars in the right mandible was performed. These postoperative hematomas developing over 2 days caused severe inspiratory dyspnea with a nonbleeding sealed extraction wound. Since an increase in factor-VIII activity to 10% was obtained only by giving three units of cryoprecipitate four times (by additional therapy with Prednisolon, Ascorbine acid and calcium), factor VIII inhibitors were supposed to have developed. Emergency tracheotomy had to be performed using local anesthesia before the quantitative proof was available (Fig. 1b). When the inhibitor titer of 40 Bethesda units/ml plasma in a factor VIII activity of less than 1% was known, treatment with the activated prothrombin complex fraction FEIBA[1] Human Immuno[2] (50 u/kg body wt. every 8 h) was initiated. Hemorrhages in the lungs and in the mediastinum required intensive bronchial care, pneumonia prophylaxis and intermittent oxygen insufflations.

After an initial increase of hematomas, the hemorrhages stopped after 2 days of causal FEIBA therapy. Thus decannulation could follow on the 5th day. With the

1 FEIBA, factor eight inhibitor bypassing activity
2 Producer: Immuno AG, Vienna



a b

Fig. 1a, b. Nineteen-year-old male patient with hemophilia A, severe course. **a** Condition following tooth extraction in the left mandible. After substitution therapy (2 years previously) cryoprecipitates are again administered. Extended hematomas of the soft tissues are present. **b** Sixteen days after a third extraction (extraction of two molars in the right mandible), extended hematomas of the tongue, the floor of the mouth and the neck are present in inhibitor hemophilia after substitution therapy with cryoprecipitates. Condition after tracheotomy

attempt to reduce the FEIBA dosage from 9000 to 3000 units/day on the 6th day of treatment bleeding expectoration recurred. Therefore the daily dosage had to be increased immediately over a period of 3 days. After administration of 75 000 FEIBA units the patient was discharged and 4 weeks later he was able to go to work.

Conclusions

Summarizing we can state that

1. Especially in maxillofacial surgery the development of inhibitor hemophilia has to be considered when extensive hemotomas occur following repeated substitution therapy. Early search for an increased inhibitor titer is necessary.
2. In hemorrhagic diathesis a tracheotomy can be successfully performed when it is indicated by fatal obstruction of the airway. Careful management becomes necessary in the case of bronchostaxis and bleeding in the mediastinum.
3. FEIBA Human Immuno was successfully administered in cases of inhibitor hemophilia. Because side effects may occur as disseminated intravasal clotting or anaphylaxis the prophylactic function of a hemophilia centre in maxillofacial surgery is of major significance.

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The Use of Fibrin Sealant (Tissucol/Tisseel) in Periodontal Surgery: Clinical and Histological Evaluation

G. P. Pini Prato, C. Clauser, and P. P. Cortellini

Key words: Fibrin, fibronectin, wound healing, periodontal surgery

Abstract

The use of fibrin sealant (Tissucol) in periodontal surgery was tested in animal experiments, which showed an increase in the number of fibroblasts in the wound 3 days after surgery. No delay in wound healing was found on histologic sections. A clinical evaluation was also carried out, with a split-mouth design at first, and as a standard procedure later. Follow-up of 128 patients up to 3 years showed no adverse effect attributable to Tissucol. Instead hemostatic and adhesive qualities of the system facilitated surgery and shortened operating times, while wound healing appeared better in the first postoperative days.

Introduction

The purpose of this paper is to illustrate the bioadhesive qualities of Tissucol as a means of fixing flaps and autografts in periodontal surgery, on the basis of previous experimental studies [6] and with the results of earlier [1, 2, 3, 5, 7] and current clinical experience.

Materials and Methods

Histologic Evaluation

Six mongrel dogs were used for histologic study. At the beginning of the study the dogs' teeth and periodontal tissue were determined to be in good health. The teeth were brushed, scaled and root planed 14 days before the study began. The test teeth in all dogs were the mandibular second premolars and first molars. Phenobarbital general anesthesia was administered to the dogs via an intravenous route; partial-thickness flaps with vertical releasing incisions were reflected on all the teeth. The flaps were extended to the mucogingival junction on the left side (test side); silk sutures were made on the right side (control side). The silk sutures were removed on the eighth postoperative day. The animals were killed; block sections were obtained at the following times: 2 h (time zero) and 1, 3, 7 and 14 days.

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Table 1. Types of procedures performed with the use of Tissucol. Follow-up durations

Procedure	Total number of patients	Number of patients with 1-year follow-up	Number of patients with 2-year follow-up	Number of patients with 3-year follow-up
Free gingival graft	51	14	18	19
Pedicle sliding graft	22	6	9	7
Modified Widman flap	38	16	13	9
Apically positioned flap	17	4	7	6
	128	40	47	41

Clinical Evaluation

One hundred and twenty-eight patients aged 8–71 years, with mucogingival problems and/or advanced periodontitis, were treated during a 3-year period with grafts, mucoperiosteal flaps and osseous therapy (Table 1). Surgical sutures were never used. All patients were examined 1 and 2 weeks and 1, 3 and 6 months postoperatively; at each examination the clinical data were collected and Kodachrome transparencies were made. In a number of patients one side of the mouth served as control, being sutured as usual [4, 5].

Results

Histologic Results

One day postsurgery: sections stained with H & E demonstrate a denser and more homogeneous coagulum on the Tissucol side than on the sutured side.

Three days postsurgery: H & E stain indicates that a greater number of fibroblasts are present on the Tissucol side than on the sutured side.

Seven days postsurgery: fibroblasts on the Tissucol side appear to be more numerous and better organized than on the sutured side. On the Tissucol side the amount of fibrin is highly decreased. Fourteen days postsurgery: both sides appear to have an equally good level of healing and tissue maturation [6].

Clinical Results

Tissucol, after its application beneath the flaps (or free grafts), (Figs. 1, 2) set within a few seconds and allowed the tissues to be positioned precisely (Fig. 3). The tissues were immediately well sealed and the biomechanical requirements were met perfectly with the flaps and the grafts maintained in the desired positions without the use of sutures or a surgical dressing. Hemostasis, in all patients, was shortened and

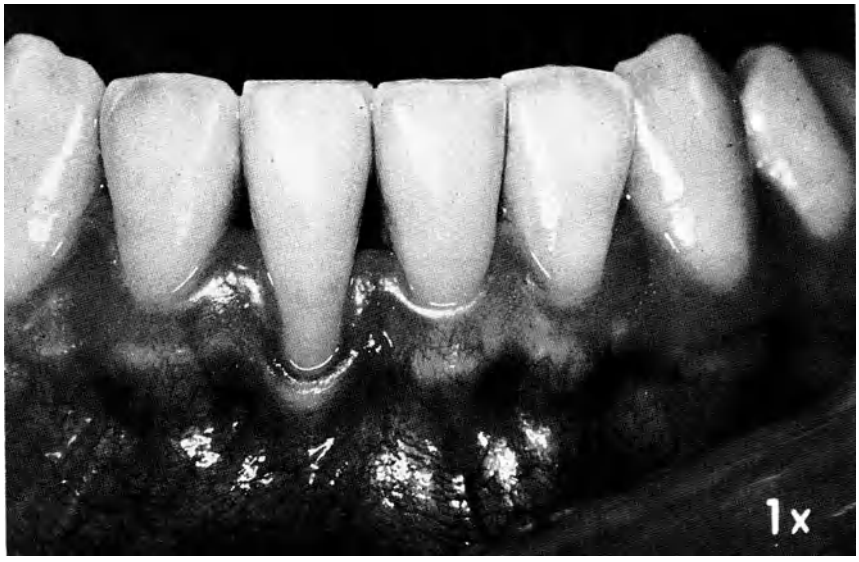

Fig. 1. Gingival recession

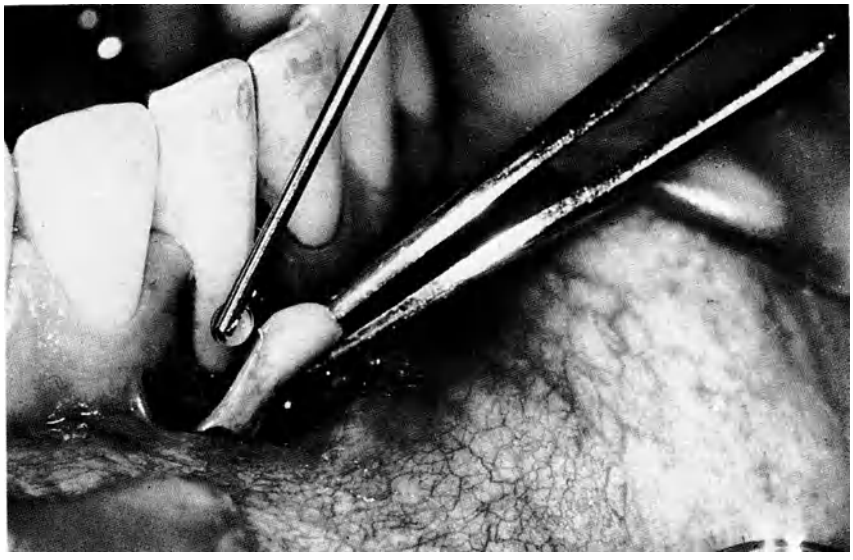

Fig. 2. The Tissucol is placed between the free graft and the recipient area

the sealed tissues showed negligible local inflammation at the 1-week postoperative observation. After 1 and 2 weeks, the healing appeared more advanced than sites sutured in a traditional way. In the patients followed up to 6 months and 1 year, the clinical course was uneventful and ideal maturation of the tissues ensued (Fig. 4).

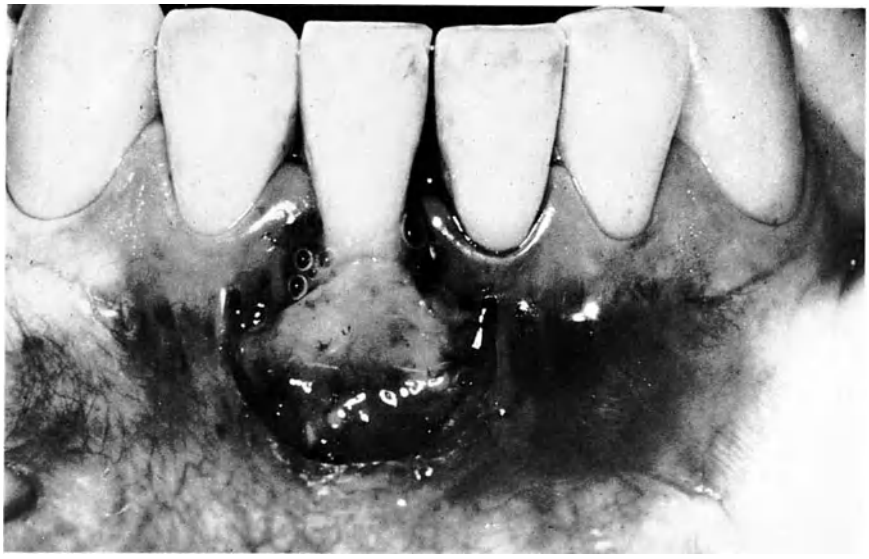

Fig. 3. The free graft is sealed after application of Tissucol

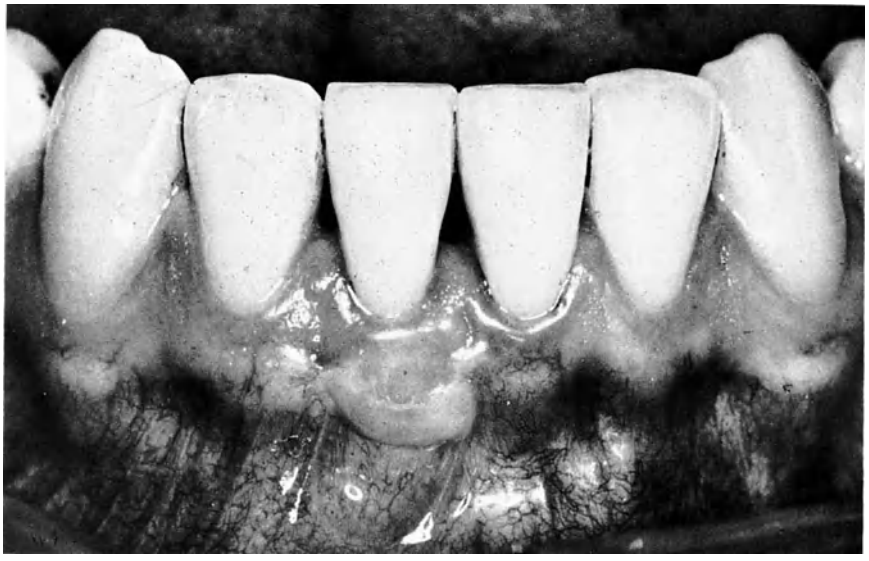

Fig. 4. Healing 1 year after surgery

Conclusions

The data resulting from these clinical and histological investigations indicated the following conclusions:

1. The use of a biologic sealing system is a simple procedure and facilitates periodontal surgery.
2. Tissucol has excellent tissue adhesive properties and is superior to silk suturing during the early (2-week) healing of periodontal wounds.

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A Modified Operating Technique Using Fibrin Sealant for Major Cysts of the Jaw in the Vicinity of the Mandibular Nerve

H. PORTEDER, V. RIEDL, E. RAUSCH, K. VINZENZ, and W. ULRICH

Key words: Jaw cyst, bone transplant, lyophilized dura, fibrin sealant

Abstract

This paper describes a modified operating technique for major jaw cysts in the immediate vicinity of the mandibular nerve. Using two groups of patients, a comparison is made of conventionally operated cysts (filling of donor bone and fibrin sealant without lyodura = control group) and a group in which the modified operating technique was used (filling of donor bone and fibrin sealant with lyodura). The technique involves covering the exposed mandibular nerve with lyodura after the cystectomy and then inserting a filling of donor bone and fibrin sealant. Postoperative checks after implementation of the new technique show better results than conventional methods.

Introduction

The fibrin sealant system was first brought to our clinic by H. Matras in 1972. Since this time selected cases of extensive jaw cysts have been treated by cystectomy and filling the osseous cystic cavity with a mixture of donor bone and fibrin sealant [5, 6]. The classical operating techniques described by Partsch in 1895 and 1910 are also used. In isolated cases plastic obturators are inserted.

Pains or malaise in the area of distribution of the nerve are not infrequently observed in patients with major cysts bordering on or displacing the mandibular nerve. In many cases these symptoms can last several months or more than 1 year. Patients complain of pain, hypoesthesia and paresthesia in the vicinity of the lower lip, sometimes extending around the jaw and to the cheek.

We decided to modify our technique in view of the fact that it was not known whether this pain was due to the surgical enucleation of the cystic sac with possible irritation of the mandibular nerve, or to the pressure exerted on the nerve by the insertion of the donor bone.

Material and Method

Over a period of 2½ years (1983–1985) we operated on 24 patients with extensive mandibular cysts in the immediate vicinity of the mandibular nerve (nervus men-

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talis). All patients were admitted to hospital. They were divided into two groups of 12, and one group was operated on in the conventional manner (control group), while the second group was given a modified operation. The objective was to reduce the postoperative pain caused by the mandibular nerve.

The surgical procedure involves the careful separation of the cystic sac from the osseous cavity [4]. This is done through a sufficiently large opening in the bone with particularly gentle exposure of the mandibular nerve, which usually lies at the base of the cyst.

The real modification involves the second step in the surgical procedure. A suitably sized piece of lyodura is laid over the exposed mandibular nerve, and the osseous cystic cavity is then filled with donor bone and fibrin sealant.

As described in the relevant literature [6, 5, 2, 9], we pulverize freeze-dried, radioactively sterilized, homologous bone supplied from the bone bank of Vienna University Orthopedic Clinic with a pestle and mortar. We try to ensure as far as possible that the grains of spongy bone are as macroscopically homogeneous as possible, with a grain diameter of about 1–2 mm. This ensures that the grains can be placed in the small recesses of large cystic cavities.

The concentration of the fibrin adhesive is as specified by Matras et al. [5]. Depending on the volume of the cyst, a suitable quantity of Tissucol is used (2.0 ml, 5.0 ml). We prefer a thrombin solution of 4 IU thrombin/ml, which has a clotting time of about 1 min, enabling large cysts to be filled layer by layer without premature setting.

The two components of the sealant, the Tissucol solution and the thrombin solution, are produced by mixing Tissucol with an aprotinin solution (9000 KIU/ml) and thrombin 4 with a calcium chloride solution. After incubation in a water bath at 37°C, it is applied simultaneously by means of a twin injection system consisting of two syringes in a holder with one needle. Kallenberger [3] recommends sufficient quantities of sealant to promote cell growth.

Modified Procedure

We proceed as follows when the mandibular nerve is exposed in its entirety or over part of its length:

First a thin layer of fibrin sealant is applied to the base of the cyst and the lyophilized dura laid on it. The dura is cut to shape and immersed in a physiological NaCl solution before insertion in the cystic cavity. This ensures that it fits exactly and molds itself to the nerve and the bone (Fig. 1).

After the fibrin sealant has set, securing the lyodura in place, the mixture of donor bone chips and fibrin sealant is applied with moderate pressure in the usual manner, thus filling the entire cavity layer by layer. Excessive filling should be avoided: the filling material should not bulge outwards, but should form a smooth contour with the bone of the jaw. The bone-fibrin sealant mixture filling the cystic cavity and the exposed jaw bone are then covered by the previously prepared mucoperiosteal flaps and the wound tightly sealed with sutures (Figs. 2–5).

The patients operated on were all adults aged 22–60 years. There were 11 follicular, 9 radicular and 4 residual cysts, which were up to 7 teeth wide. In view of

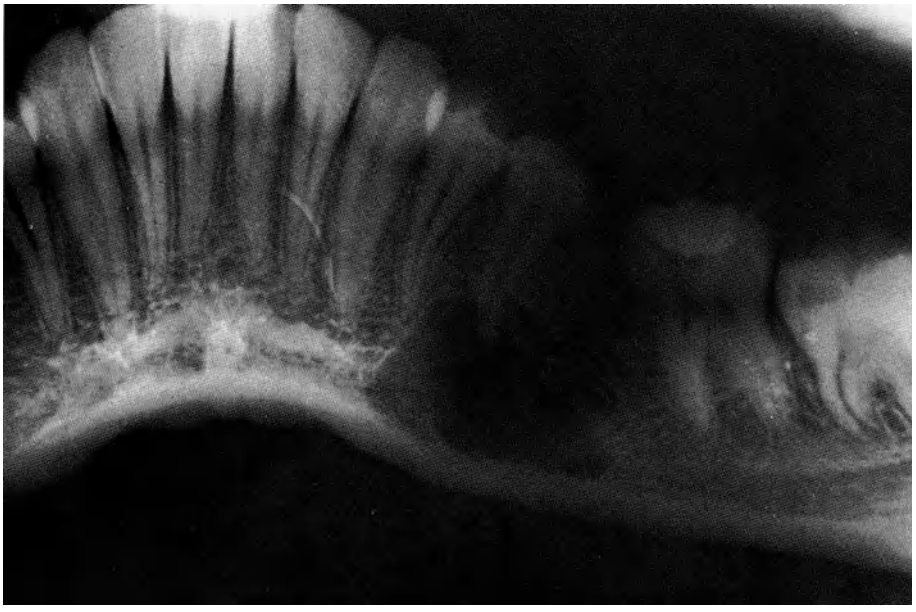

Fig. 1. Cross-section through the mandible

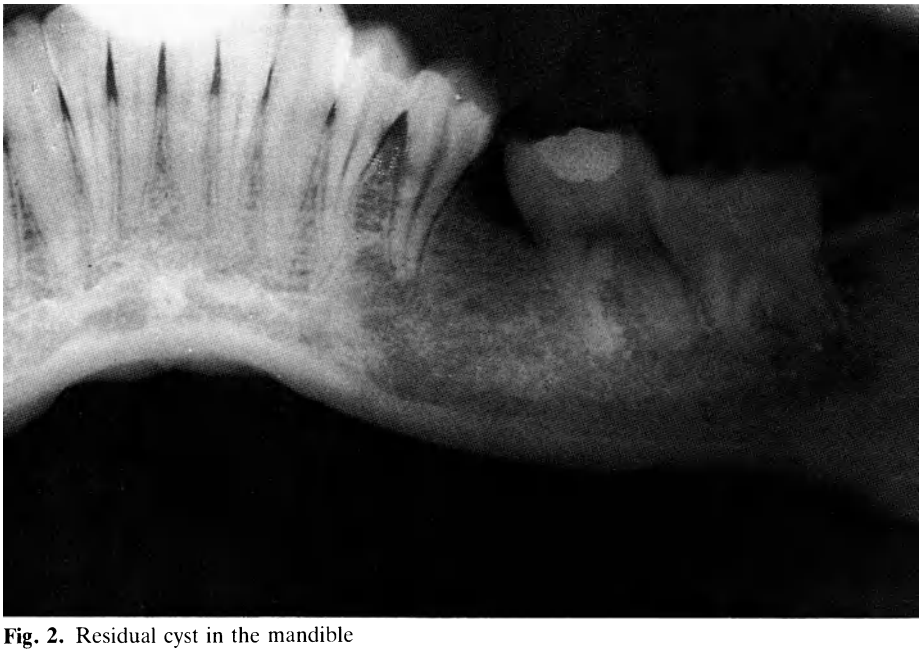

Fig. 2. Residual cyst in the mandible

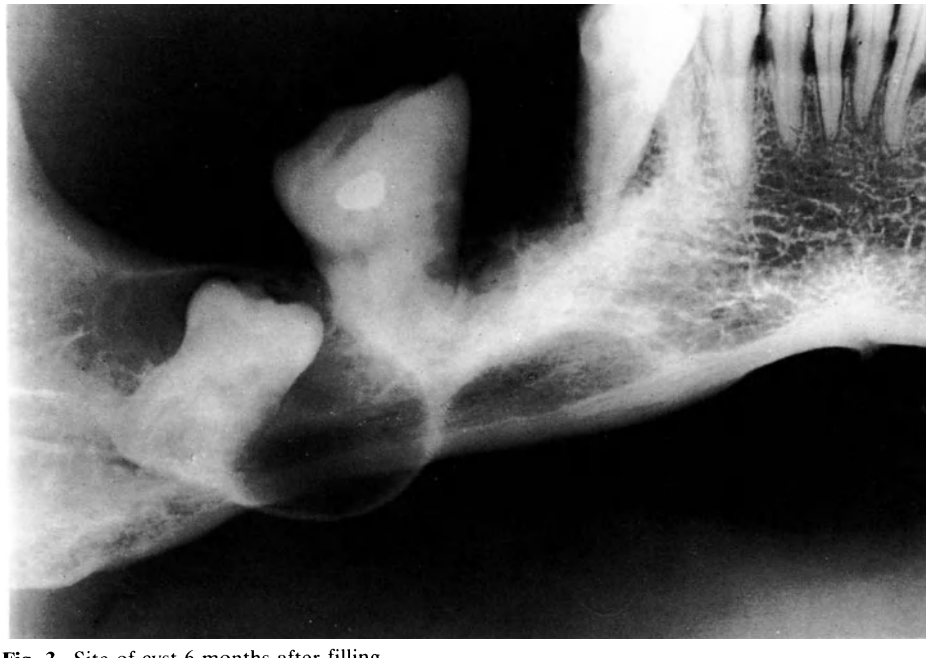

Fig. 3. Site of cyst 6 months after filling

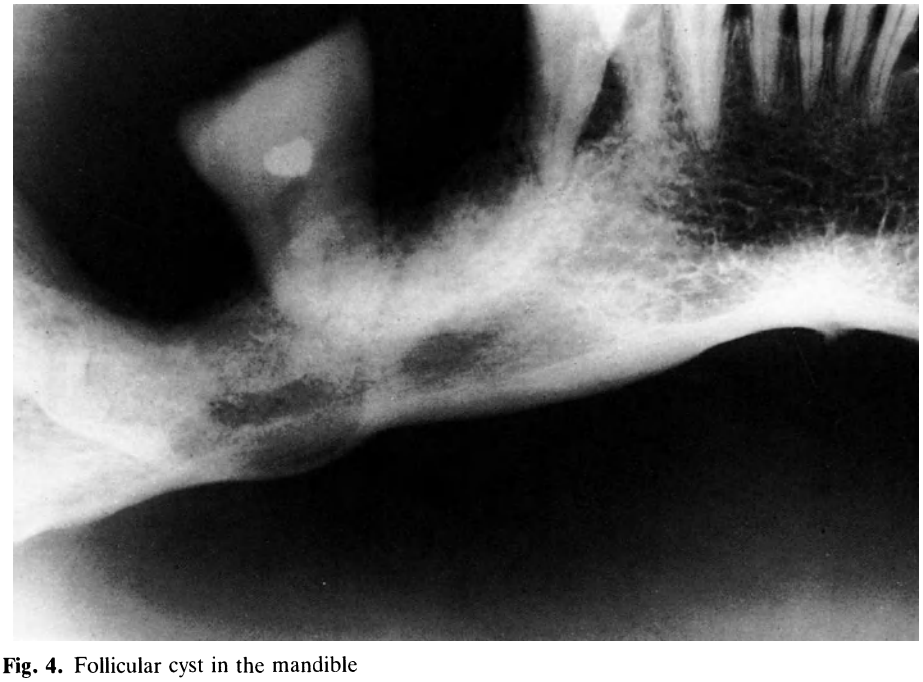

Fig. 4. Follicular cyst in the mandible

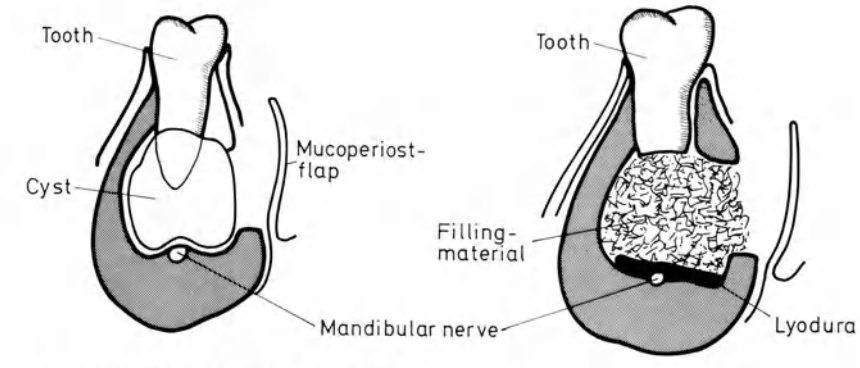

Fig. 5. Site of cyst 10 months after filling

the fact that all patients had been admitted, it was possible to monitor both groups continuously until the 18 day postoperatively. Thereafter outpatient checks were carried out after 3–4 weeks, 6–8 weeks, and 3, 6 and 12 months. Radiographs were taken immediately postoperatively and after 3, 6 and 12 months.

Results

In comparing the two groups, we noticed that during the first days postoperatively patients' comments referred principally to the pain which they felt. Patients in both groups complained of more or less severe postoperative pain, but it was scarcely possible to define the nature of the malaise more closely, e.g., "burning feeling," paresthesia or hypoesthesia.

Due to patients' vague qualification and quantification of the pain and their imprecise descriptions of sensations, it was impossible during the first few days postoperatively to draw any definite conclusions about the nature and degree of any possible irritation of the mandible with functional impairment. Even the sensitivity test using a pointed probe on the lower lip only provided limited information because of the postoperative swelling.

Only after their wounds had completely healed were patients able to describe local sensations more exactly. Thus about 3–4 weeks postoperatively we established dysesthesia and hypoesthesia at the site of the operation and in the distribution area of the mandibular nerve in seven of the patients in *group 1* (without lyodura covering the nerve). Hypoesthesia was still present in five patients after 3–6 months and in three patients even after 12 months. However, all patients noted a steady improvement over the course of the follow-up period (Table 1).

In *group 2* (where the nerve had a covering of lyodura), the evaluation of sensitivity and pain during the first days postoperatively hardly varied from that of group 1. However, thereafter a difference became apparent. After 3–4 weeks, only four patients in group 2 were still affected by diysesthesia and hypoesthesia, compared with seven patients in group 1.

Table 1. Group 1 (conservative treatment, without lyodura covering on the nerve)

Patient	1–3 days	4–10 days	3–4 weeks	3 months	6 months	12 months
1	++	+(x)	x	−	−	−
2	++	+(x)	−	−	−	0
3	+	0	0	0	0	0
4	+	0	0	0	0	0
5	+	+(x)	x	0	0	0
6	++	+(x)	x	−	0	0
7	+	0	0	0	0	0
8	0	0	0	0	0	0
9	+	0	0	0	0	0
10	++	+−	−	−	−	−
11	++	+−	−	−	−	−
12	+	+	−	0	0	0

0, no unpleasant sensations; +, pain; x, malaise (paresthesia, burning feeling); −, hypoesthesia

Table 2. Group 2 (modified treatment, with lyodura covering on the nerve)

Patient	1–3 days	4–10 days	3–4 weeks	3 months	6 months	12 months
1	+	0	0	0	0	0
2	+	+	−	0	0	0
3	++	+	x	−	0	0
4	+	0	0	0	0	0
5	0	0	0	0	0	0
6	+	0	0	0	0	0
7	+	0	0	0	0	0
8	0	0	0	0	0	0
9	++	+	x	−	−	0
10	+	0	0	0	0	0
11	+	+	−	0	0	0
12	+	+−	0	0	0	0

0, no unpleasant sensations; +, pain; x, malaise (paresthesia, burning feeling); −, hypoesthesia

The difference became even more pronounced after 3 months (two patients in group 2 mentioned hypoesthesia compared with five patients in group 1). After 6 months, one patient in group 2 still complained of slight hypoesthesia, as against four patients in group 1.

A year after the operation, all the patients in group 2 were without pain, while three patients in group 1 were still affected by slight hypoesthesia (Table 2).

Complications

Reoperation was required in one case in group 1 4 weeks postoperatively, when a tooth (third lower left) had to be resected. The reoperation was necessitated by the

formation of fistulae in region 33 and the loss of bone fragments. A second patient in group 1 had a parodontally damaged tooth adjacent to the operation site drawn 6 months postoperatively after the tooth had been the cause of continual inflammation. This patient also lost bone fragments from time to time. Four other patients were still losing bone fragments 3 months postoperatively, but no therapy was required.

Discussion

This modified operating technique involves covering the mandibular nerve, which may be partly or completely exposed, with lyodura after cystectomy in the mandible. On the condition that the cystic sac is carefully removed and the mandibular nerve exposed as gently as possible, our investigations were based on the assumption that the pain frequently encountered postoperatively was due to the pressure of the rough filling material on the mandibular nerve. For this reason we slightly modified the operation. The exposed mandibular nerve is covered by a layer of lyodura, which is fixed in position using fibrin sealant. The nerve is thus protected from the pointed, sharp-edged bone chips of the filling material. The superior results obtained appear to be due primarily to this procedure, though careful filling in thin layers using only moderate pressure also appears to have played a role.

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