

Ureteral Physiology: Rationale for Medical Therapy of Ureteral Calculi

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UBC Urology Grand Rounds
April 4, 2007



Objectives

1. Ureteral physiology
2. Review how ureteral stones cause pain
3. MOA of commonly used analgesics
4. Evidence for analgesics in renal colic
5. Spontaneous stone passage
6. Rationale for medical expulsive therapy
7. Evidence for medical expulsive therapy

Ureteral Anatomy

- 22-30cm long
- Urothelium + Lamina propria = Mucosal lining
- Inner longitudinal smooth muscle
- Outer circular smooth muscle
- Adventitia

Mucosal Layer

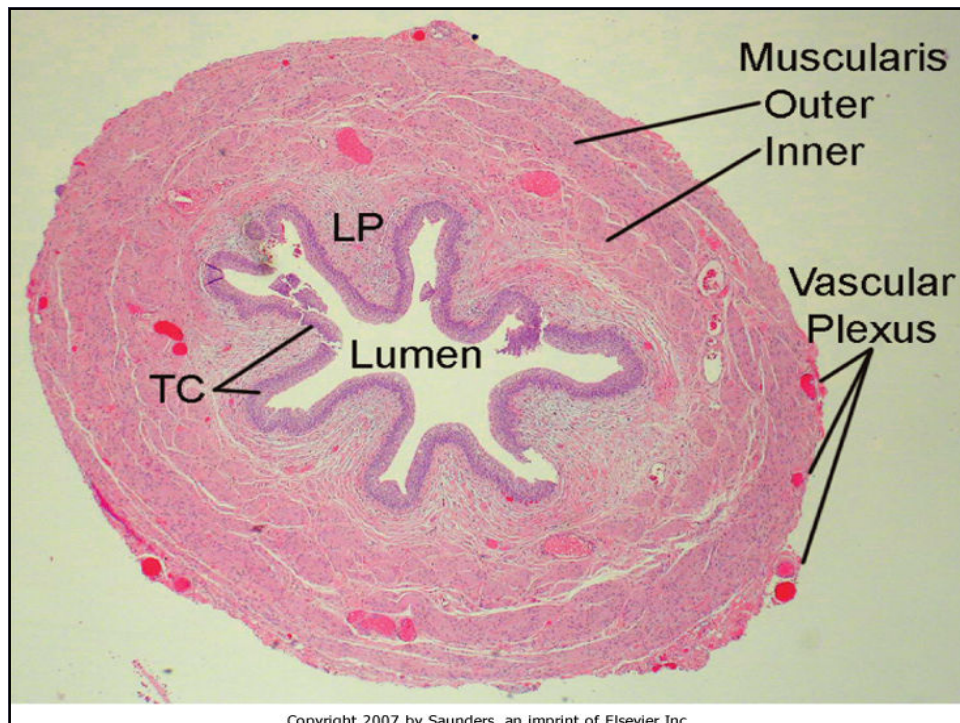
- Transitional epithelium
- Barrier
- Urothelium interacts with smooth muscle
- Lamina propria

Mucosal Layer

- Transitional epithelium
- Barrier
- Urothelium interacts with smooth muscle
- Lamina propria
 - Nerve endings
 - Capillaries

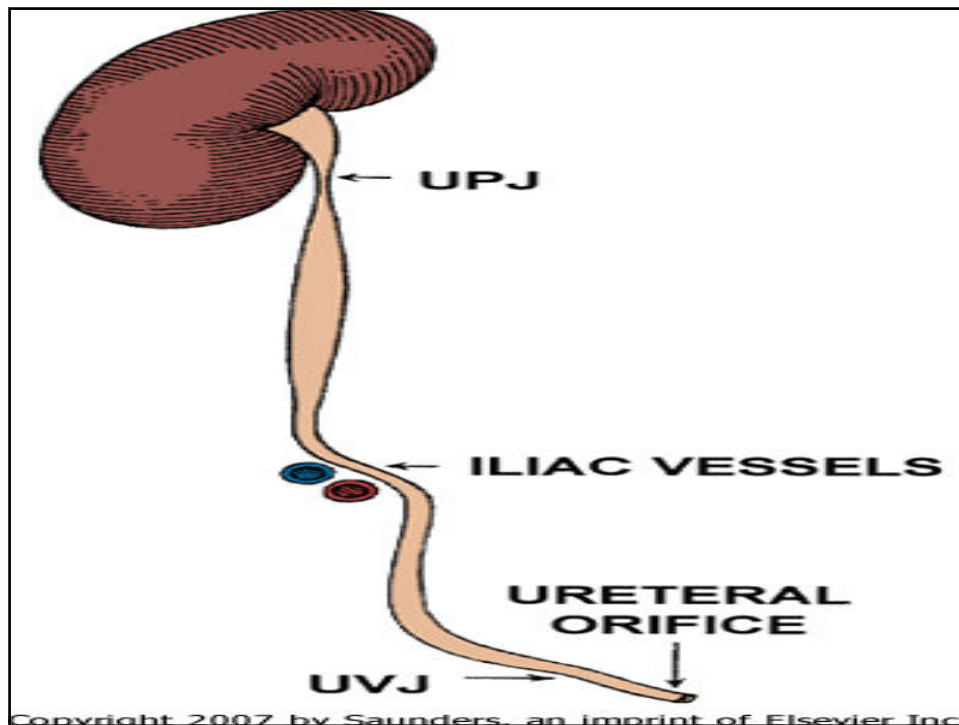
Muscular Layer

- Inner longitudinal
- Outer circular
- Structural support
- Function - peristalsis



Ureteral Caliber

1. UPJ
2. Iliac vessels
3. UVJ



Ureteral Nomenclature: Endoscopic

Distal to iliac vessels

Proximal to iliac vessels

Ureteral Nomenclature: Radiological

- Proximal: Renal pelvis to upper sacrum
- Middle: Upper to lower sacrum
- Distal: Lower sacrum to bladder












Ureteral Physiology

1. Obstruction
2. Peristalsis
3. Innervation
4. Pain transmission

Obstruction: Variables

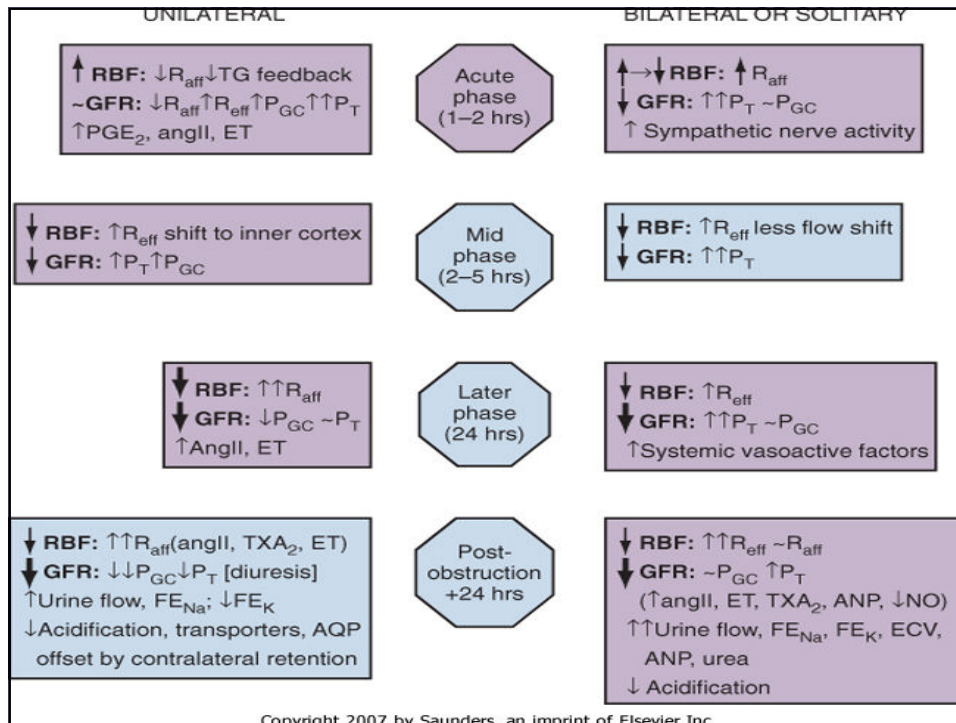
- Extent and severity
- Unilateral or bilateral
- Duration

Unilateral Ureteric Obstruction

Time	RBF	GFR	Pt	Mediators
1-2 hrs				PGE2, NO, AII, ET
2-5 hrs				AII, ET
24 hrs				AII, ET

Bilateral Ureteric Obstruction

- Less initial vasodilation
- Greater decrease in RBF
- Greater vasoconstriction
- Lacks shift of blood flow from cortex to medulla
- $\uparrow P_t$: More profound and prolonged
- Vasoactive substances unable to secrete through contralateral kidney



Peristalsis

- Pacemaker in minor calyx
- ANS not required – modulator
- Electrical propagation
- Myogenic in origin
- Organized contraction / relaxation of inner and outer smooth muscle
- Rate decreases from proximal to distal (increases again at UVJ)

Peristalsis

- 3 types of smooth muscle cells
 - 1) Atypical cells (Pacemakers)
 - 2) Interstitial cells (Modulators)
 - 3) Typical cells (Propagators)

Modulators of Peristalsis

- Diuresis / Urine Volume / Stretch
- SNS
- PNS
- PG's
- Tachykinins (Substance P, Neurokinin A/B)
- Calcitonin gene related peptide

Peristalsis: PNS

- S2-S4 pelvic splanchnic nerves
- Cholinergic
- Cholinergic agonists increase contractile force
- Cholinergic agonists increase frequency
- Compared to bladder minimal effect
- Poor therapeutic target

Peristalsis: SNS

- T10 – L2 preganglionic
- Postganglionic from aorticorenal, superior and inferior hypogastric plexus
- Alpha receptors – contraction
- Beta receptors - relaxation
- NE typically effects alpha > beta
- SNS stimulation results in ureteral contraction

Ureteral Sensory Nerves

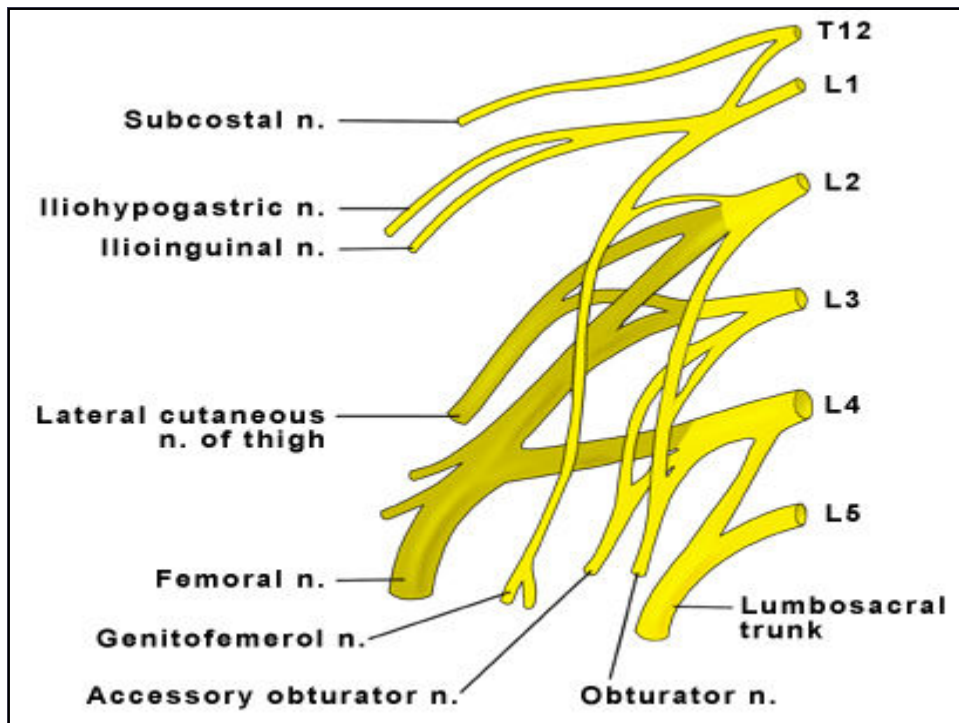
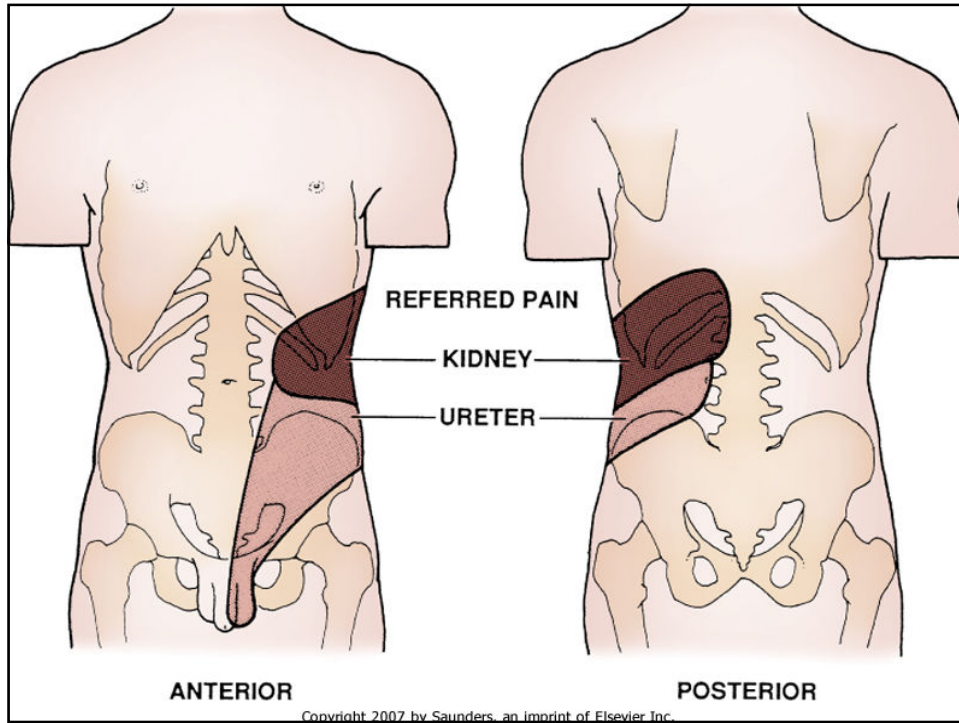
- Visceral afferent nerves follow sympathetics and parasympathetics
- Renal a, aorticorenal, superior mesenteric and celiac ganglia
- Splanchnic nerves
- Spinal dorsal root ganglia
- Anterolateral spinal column

Ureteral Sensation: Pain Fibers

1. A delta fibers poorly myelinated
 - “fast” sharp pain
 - typically mechanical or thermal pain
2. C fibers unmyelinated
 - “slow” chronic pain
 - typically chemical stimuli
 - main transmitters of visceral pain

Sensation: Referred Pain

- Visceral sensory nerve afferents from ureter synapse in ganglia
- Stimulate other somatic nerves from similar spinal segment
- Subcostal, ileoinguinal, ileohyogastric, genitofemoral nerves



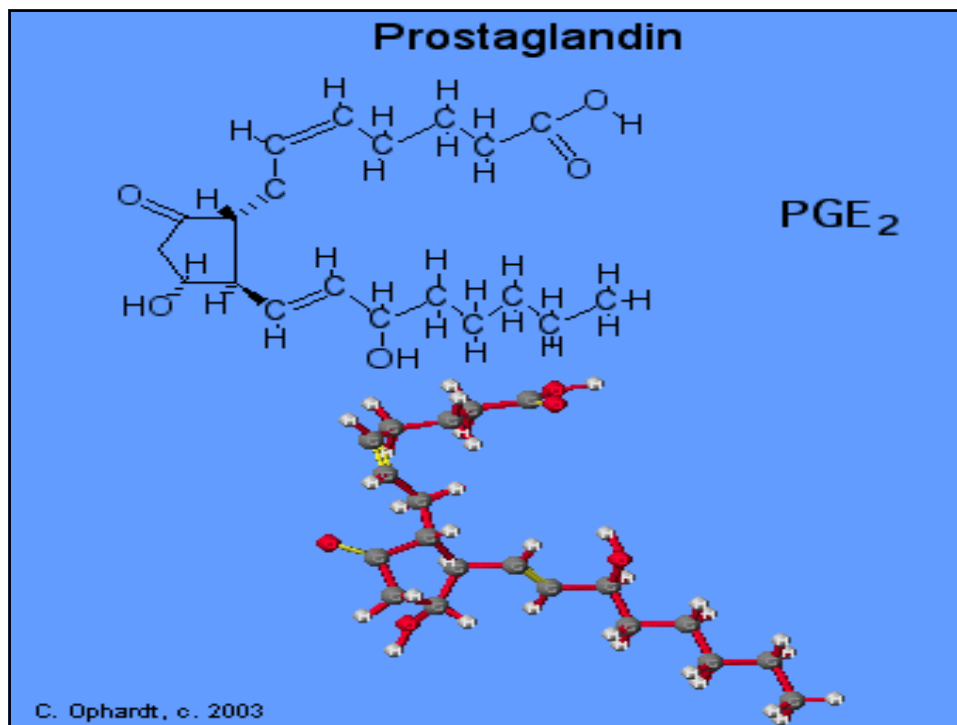
How does a ureteral calculus cause pain?

1. Obstruction \longrightarrow distension of renal capsule, collecting system, ureter
2. Mucosal irritation \longrightarrow noxious stimuli
3. Reflex ureteral spasm \longrightarrow renal colic

Renal Colic : Ureteral Spasm

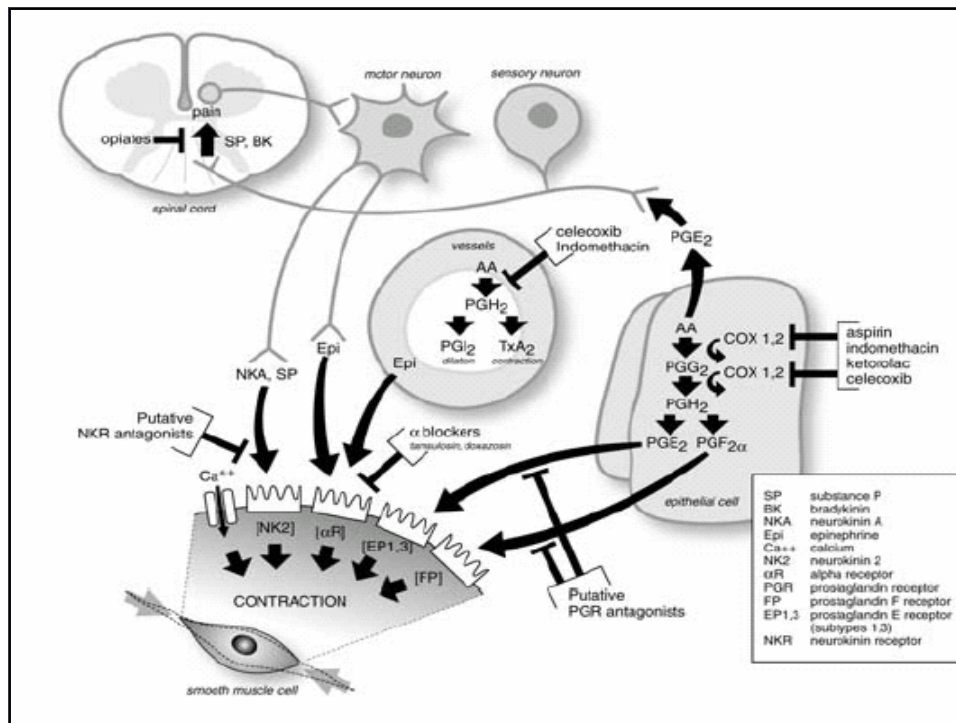
- Obstruction \longrightarrow Distension \longrightarrow Release of bradykinin, tachykinins, PG's
- \uparrow Peristalsis \longrightarrow \uparrow Distension
- Local irritation
- Increased amplitude
- Decreased frequency
- Eventually decreased pressure
- Decreased urine flow rates

Therapeutic Targets



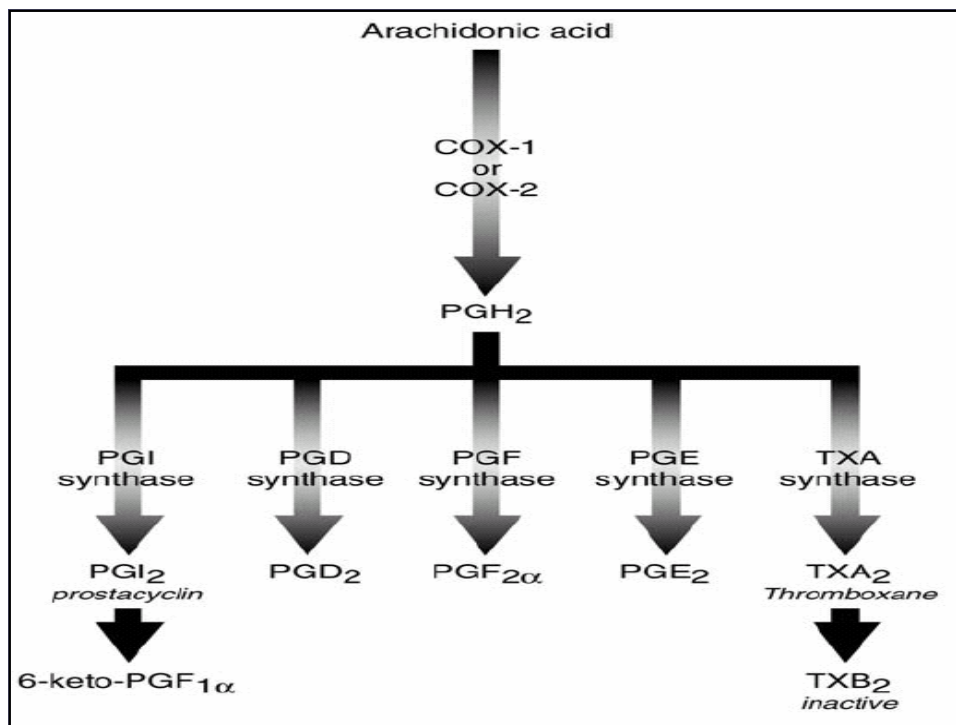
Prostaglandins: Functions

1. Increase RBF via afferent arteriole VD
2. Modulate peristalsis
3. Pain mediator
4. Vascular permeability
5. Chemotaxis



Prostaglandin Synthesis

- Membrane phospholipids
- Arachadonic acid
- Cyclooxygenase pathways
- Lipoxygenase pathways



Analgesics for Renal Colic

1. Conventional
2. Alternative

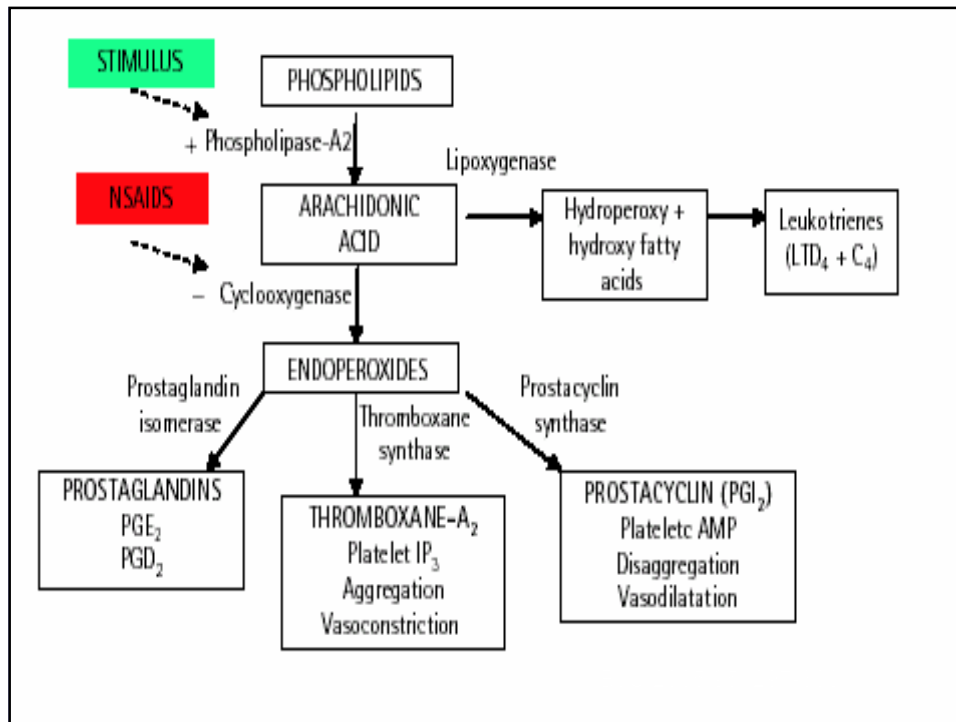
Conventional analgesics for renal colic

1. Opioids
2. NSAIDS
 - COX nonselective
 - COX II selective

Alternative analgesia for renal colic

1. Corticosteroids
2. Anti-histamines
3. Anti-muscurinics
4. Phosphodiesterase inhibitors
5. DDAVP
6. Nitrates
7. *Calcium channel blockers*
8. *Alpha adrenergic blockers*
9. Subcostal nerve blocks
10. Local active abdominal warming
11. Acupuncture
12. TENS

NSAIDS Mechanism of Action



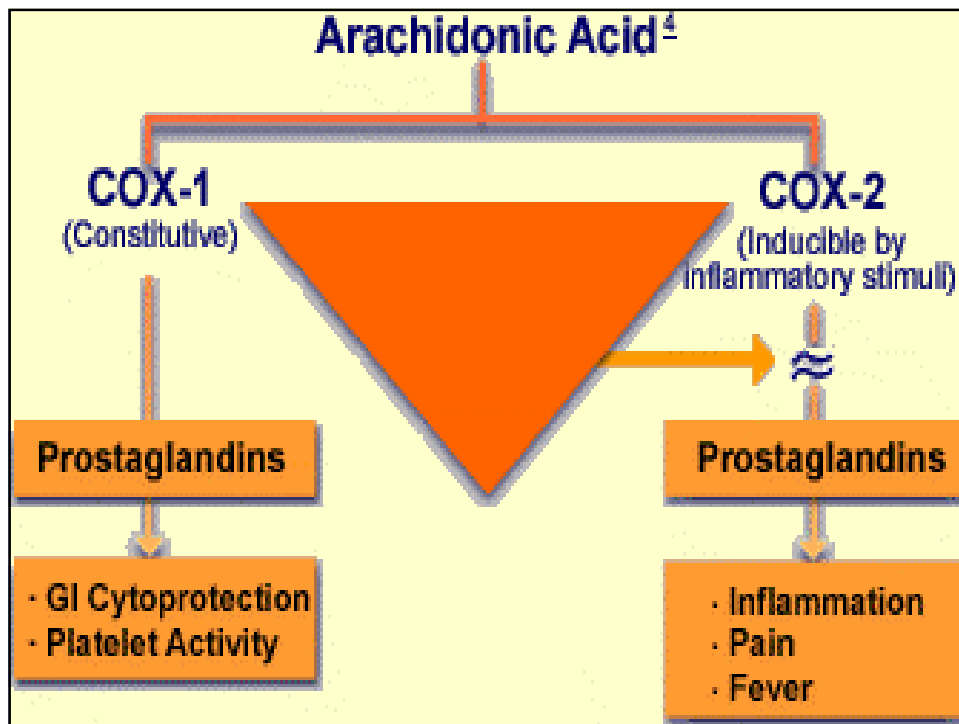
Doses, Side Effects and Contraindications of Common NSAIDS

Class and Name of Drug	Adult Dose	Adverse Effects	Contraindications
NSAIDs			
Ketorolac	30–60 mg IV or IM loading dose, then 15 mg IV or IM every 6 hr; oral continuation dose: 10 mg orally every 4–6 hr (maximum, 40 mg/day), not to exceed 5 days†	Common: dyspepsia, nausea, abdominal pain, diarrhea, headache, dizziness, elevated aminotransferase levels, drowsiness, tinnitus, pain at injection site Rare but serious: anaphylaxis, gastrointestinal bleeding, acute renal failure, bronchospasm, interstitial nephritis, Stevens–Johnson syndrome, agranulocytosis	Absolute: hypersensitivity, active peptic ulcer disease, cerebrovascular hemorrhage, breast-feeding, 3rd trimester of pregnancy Relative: advanced age, hypertension, congestive heart failure, nasal polyps, volume depletion
Diclofenac	50 mg orally 2 or 3 times/day	Thrombocytopenia; others similar to those of ketorolac	Similar to those for ketorolac

Teichman NEJM 2004 350:684-93

COX 2 Selective NSAIDS

- 2 isoforms of cyclooxygenase
- COX 1 constitutively expressed
- COX 2 inducible by inflammation and mechanical stimuli
- Non-selective NSAIDS inhibit 1 and 2
- COX 2 selective \implies less side effects
- Possible increase in adverse CVS events



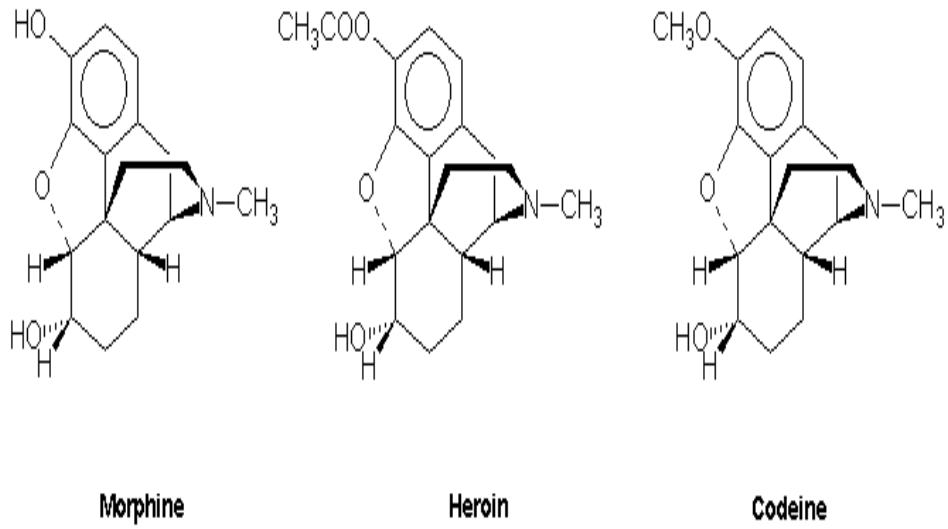
Cyclooxygenase-2 inhibitors			
Rofecoxib	50 mg/day	Common: diarrhea, hypertension, nausea, epigastric discomfort, peripheral edema, dyspepsia, fatigue, dizziness Rare but serious: gastrointestinal bleeding, esophagitis, hypersensitivity, bronchospasm, hypertension, congestive heart failure, potentially increased risk of myocardial infarction, hepatotoxicity, blood dyscrasias, renal failure	Absolute: hypersensitivity, NSAID-induced asthma, hepatic failure, renal failure, 3rd trimester of pregnancy, peptic ulcer disease, gastrointestinal bleeding Relative: renal failure, liver failure, hypertension, ischemic coronary artery disease, dehydration, congestive heart failure, fluid retention, advanced age

Teichman NEJM 2004 350:684-93

NSAIDS

- Block afferent arteriole vasodilation \longrightarrow
Prevent Pt pressure increase
- Reduce diuresis
- Reduce edema
- Reduce ureteral spasm
- Reduce pain transmission

Opioids



Opioids: Mechanism of action

- Mu receptors
- Brain, spinal cord, peripheral nerves, ganglia, adrenal medulla, gut

Narcotics			
Meperidine	1 mg/kg of body weight IM every 3–4 hr	Common: dizziness, lightheadedness, sedation, nausea, vomiting, dysphoria, dry mouth, urinary retention, hypotension, agitation, disorientation, constipation, flushing Rare but serious: respiratory depression, respiratory arrest, seizure, cardiac arrest, arrhythmia, shock	Absolute: hypersensitivity, use of monoamine oxidase inhibitors within 14 days Relative: advanced age, respiratory depression, seizure disorder, liver failure, renal failure, hypothyroidism
Morphine sulfate	0.1 mg/kg IM or IV every 4 hr	Biliary spasm, paralytic ileus, toxic megacolon, increased intracranial pressure, miosis, bradycardia; others similar to those of meperidine	Absolute: hypersensitivity, paralytic ileus Relative: chronic obstructive pulmonary disease, biliary disease, acute alcoholism
Narcotic combinations			
Acetaminophen with codeine	300 mg of acetaminophen with 30 mg of codeine, 2 tablets orally every 4–6 hr	Common: lightheadedness, sedation, dizziness, constipation, nausea, vomiting, hypotension, rash, biliary spasm, urinary retention, miosis Rare but serious: pancytopenia, thrombocytopenia, liver damage, respiratory depression, hemolytic anemia, neutropenia	Absolute: hypersensitivity Relative: glucose-6-phosphate dehydrogenase deficiency

Teichman NEJM 2004 350:684-93

Opioids: Advantages and Disadvantages

Advantages	Disadvantages
Inexpensive	Don't act on source of pain
Familiarity	Drug seeking
Titratable	Dependence / Addiction
Reversible	
Oral / IV	
Potent	

NSAIDs: Advantages and Disadvantages

Advantage	Disadvantage
Act on source of pain	Less titratable
Lower ureteral spasm	Severe side effects
Inexpensive	Slower onset?
Oral / IV	Less potent?

Analgesics for renal colic: Evidence

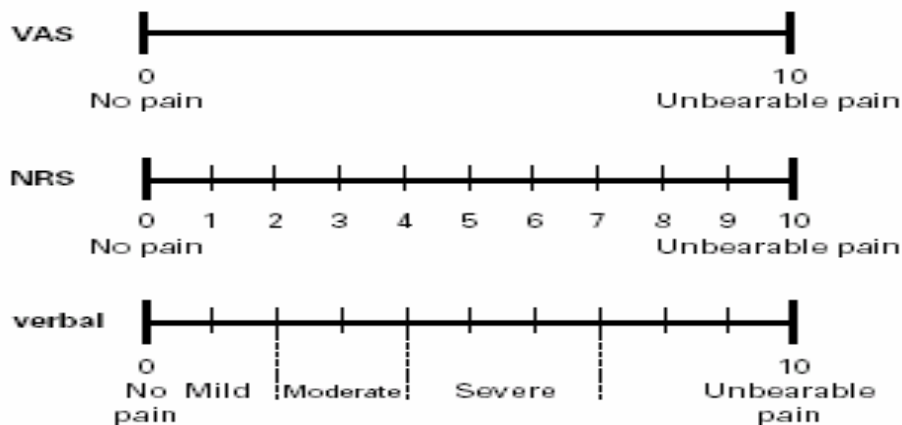


Fig. 1. Pain measurement with different methods.

BJU 2002 90: 481-488

Comparison of Intravenous Ketorolac, Meperidine, and Both (Balanced Analgesia) for Renal Colic

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Thomas J Maneatis, MD*
Ronald H Lewis, MD[‡]
Lincoln Bynum, MD*
David R Nelson, MS[‡]

AUGUST 1996 28:2 ANNALS OF EMERGENCY MEDICINE

Study objective: To compare the analgesic efficacy and safety of IV ketorolac, the only nonsteroidal antiinflammatory drug indicated for parenteral use in acute pain in the United States, with IV meperidine and with a combination of the two agents in renal colic.

Methods

- Double blind multi-center RCT
- Group 1: Ketorolac and placebo
- Group 2: Meperidine and placebo
- Group 3: Both
- VAS scale and Categorical Scale
- Drug tolerability and functional impairment

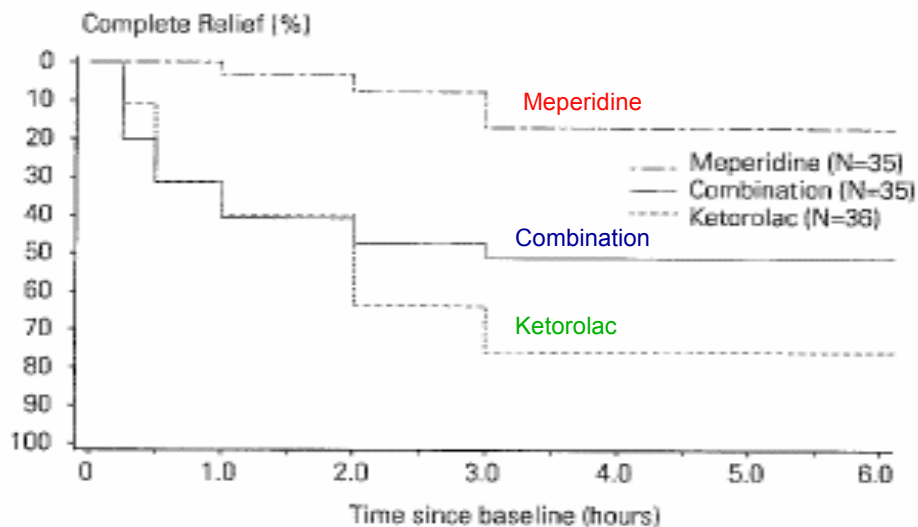
Table 2.

Mean pain-intensity scores and pain-relief scores for first 30 minutes of study.

Parameters	Meperidine	Ketorolac	Combination	Overall	P		
					Meperidine Versus Ketorolac	Meperidine Versus Combination	Ketorolac Versus Combination
VAS, pain-intensity score (100-mm scale)							
0 Minutes	77.4±3.6	80.3±3.5	73.3±3.3	.21	.52	.30	.08
15 Minutes	55.0±4.3	34.8±4.5	25.8±4.5	<.001	.003	<.001	.10
30 Minutes	56.6±5.2	24.7±4.6	23.5±4.7	<.001	<.001	<.001	.87
Categorical pain-severity score (0, none; 3, severe)							
0 Minutes	2.7±.1	2.8±.1	2.7±.1	.63	.40	.44	.95
15 Minutes	1.9±.1	1.4±.1	1.1±.1	<.001	.02	.001	.11
30 Minutes	2.1±.1	1.1±.1	.9±.2	<.001	<.001	<.001	.27
Categorical pain-relief scores (0, none; 5, complete)							
15 Minutes	1.6±.2	2.5±.2	2.9±.1	<.001	<.001	<.001	.17
30 Minutes	1.5±.2	2.8±.2	2.6±.2	<.001	<.001	<.001	.59

Figure 1.

Kaplan-Meier curve for time elapsed before complete relief of pain for the entire study period.



Cordell et al Summary:

- Ketorolac better than meperidine for:
 - overall pain relief
 - time to pain relief
 - time to supplemental meperidine
 - number requiring supplemental meperidine
- Ketorolac and combination groups had similar efficacy in all categories

Cordell et al Summary:

- No significant advantage of combined therapy
- 2/3 of ketorolac and combination group still required supplemental meperidine
- “Balanced analgesia”
- NSAID should be first choice for analgesia

PAIN MANAGEMENT/ORIGINAL RESEARCH

Intravenous Morphine Plus Ketorolac Is Superior to Either Drug Alone for Treatment of Acute Renal Colic

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Linda C. Degutis, DrPH
Keala Landry, MD
Swarupa R. Vedere, MD
Harry C. Moscovitz, MD
Gail D'Onofrio, MD

From the Section of Emergency Medicine, Yale University School of Medicine, New Haven, CT (Safdar, Degutis, Moscovitz, D'Onofrio); the Department of Emergency Medicine, The Mount Sinai School of Medicine, New York, NY (Landry); and the Department of Medicine, Hospital of Saint Raphael, New Haven, CT (Vedere).

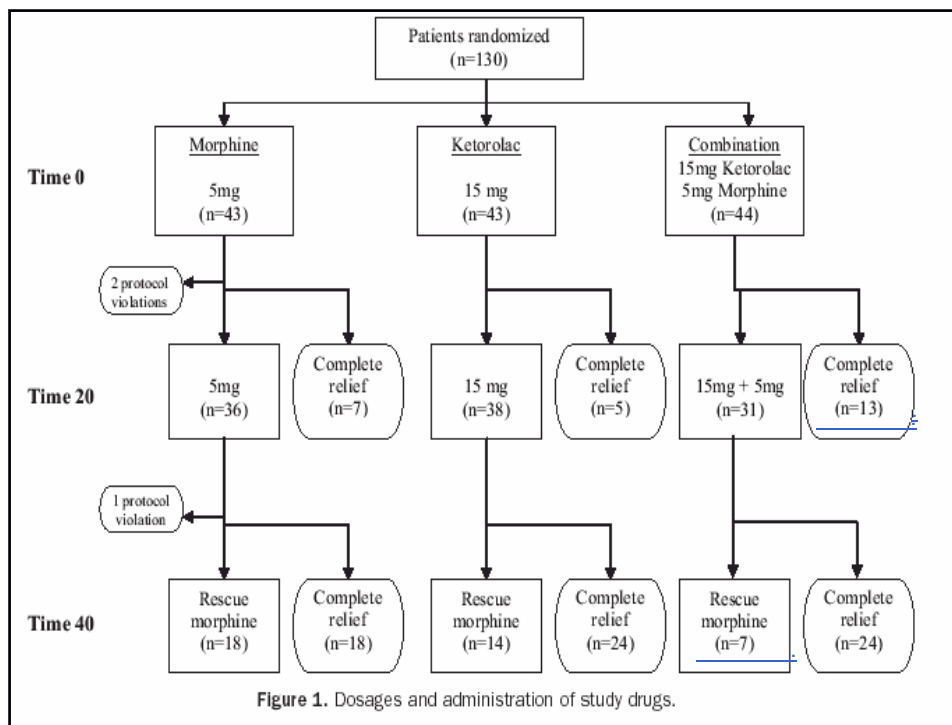
Volume 48, NO. 2 : August 2006

Annals of Emergency Medicine 173

Intravenous Morphine Plus Ketorolac Is Superior to Either Drug Alone for Treatment of Acute Renal Colic

Methods

- Prospective double blind RCT
- Group 1: Morphine
- Group 2: Ketorolac
- Group 3: Both
- VAS and Categorical Pain Scale
- Primary outcome was pain and need for rescue analgesia by 40 minutes



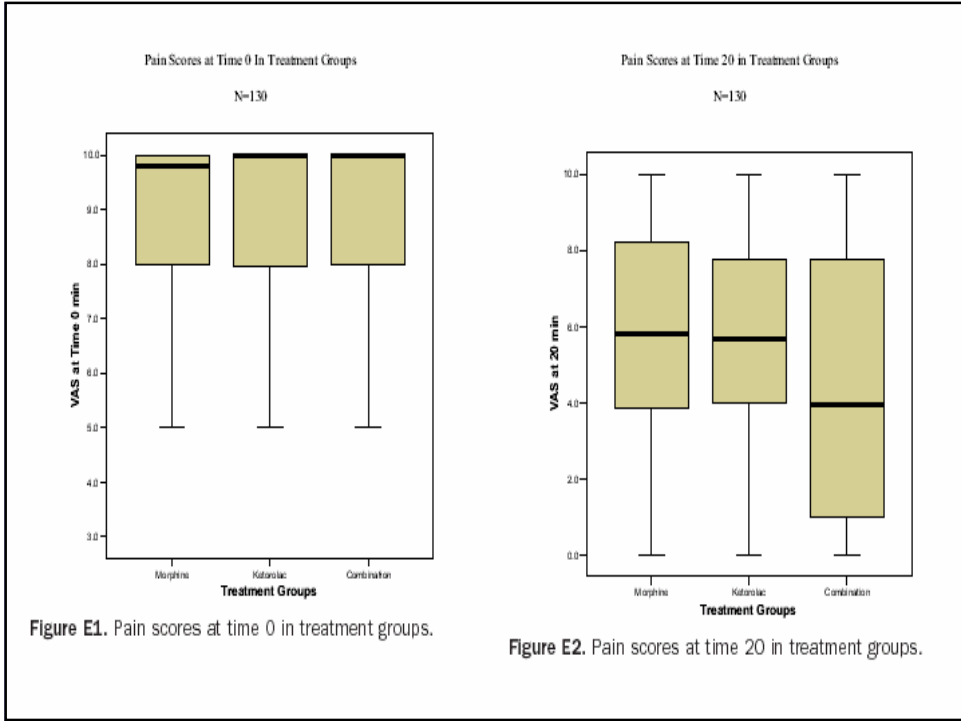


Figure E1. Pain scores at time 0 in treatment groups.

Figure E2. Pain scores at time 20 in treatment groups.

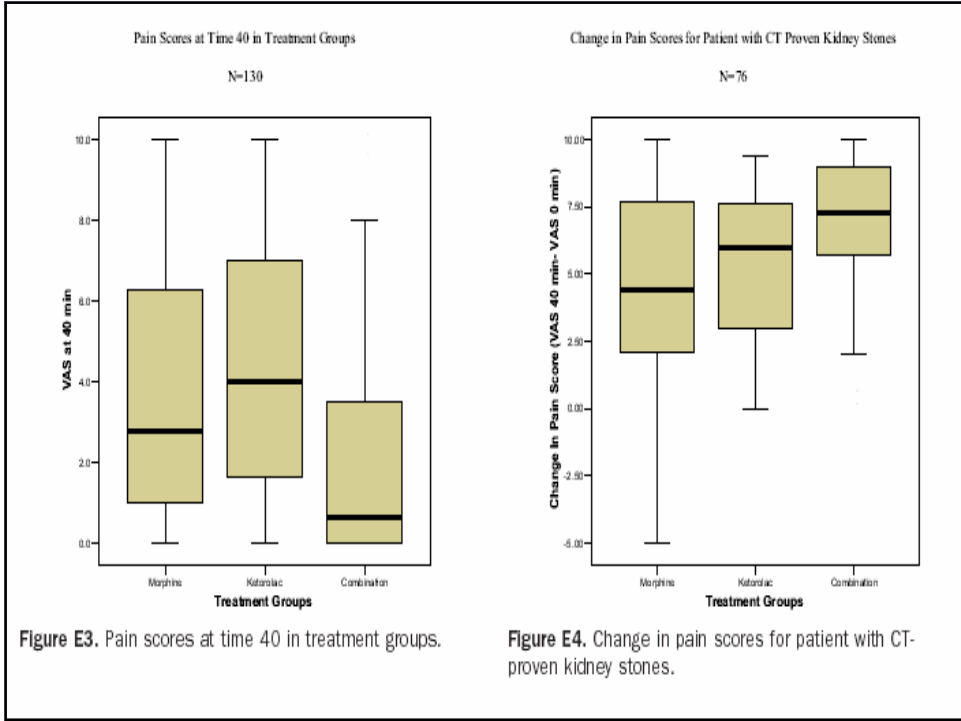


Figure E3. Pain scores at time 40 in treatment groups.

Figure E4. Change in pain scores for patient with CT-proven kidney stones.

Safdar et al Summary:

- 30mg Ketorolac = 10mg morphine
- Morphine \longrightarrow titratable
- Morphine \longrightarrow more side effects
- Combined morphine and ketorolac better than either alone + fewer SE's
- No significant difference between morphine and ketorolac groups unlike many other trials
-

AUAUS 2006 Lesson 17 Summary

Comparison of NSAIDS to Narcotics

TABLE 1. *Randomized studies of NSAIDs and narcotics in renal colic*

References	No. Pts	Agents Studied (dose)	Outcomes/Comments	Conclusions
Torralba et al ⁷¹	48	Ketorolac (30 mg IM), tramadol (1 mg/kg SC)	No significant difference in outcomes (success in >80%) or side effects, ketorolac significantly more effective 15 mins after injection	Both drugs effective but ketorolac had quicker onset
Larkin et al ⁷²	70	Ketorolac (60 mg IM), meperidine (100–150 mg IM)	Ketorolac significantly ($p < 0.05$) more effective at 40, 60, 90 mins; no difference in later operations or admissions	Ketorolac significantly more effective more rapidly
Sandhu et al ⁷³	76	Ketorolac, pethidine narcotic	88% Both groups had improved symptoms at 1 hr but ketorolac significantly better, 56% ketorolac group needed rescue vs 74% pethidine group	Ketorolac is a viable alternative to pethidine
Cordell et al ⁷⁴	154	Ketorolac (60 mg IM), meperidine (50 mg IM), both	50% Decrease in pain at 30 mins for 75% ketorolac, 74% combination, 23% meperidine	Ketorolac or combination better than meperidine alone
Eray et al ⁷⁵	47	Tramadol (50 mg IV), meperidine (50 mg IV), meperidine given for rescue in both groups (50 mg)	Visual analog scores at 15 and 30 mins significantly better in meperidine group	Meperidine 50 mg superior to tramadol 50 mg
Oosterlinck et al ⁷⁶	121	Ketorolac (10 mg IM), ketorolac (90 mg IM), pethidine narcotic (100 mg IM)	Further treatments required within 10 hrs for 17% ketorolac 90 mg, 39% ketorolac 10 mg, 47% pethidine	IM ketorolac efficacious for treating renal colic

AUAUS 2006 Lesson 17

BMJ Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic
 Anna Holdgate and Tamara Pollock

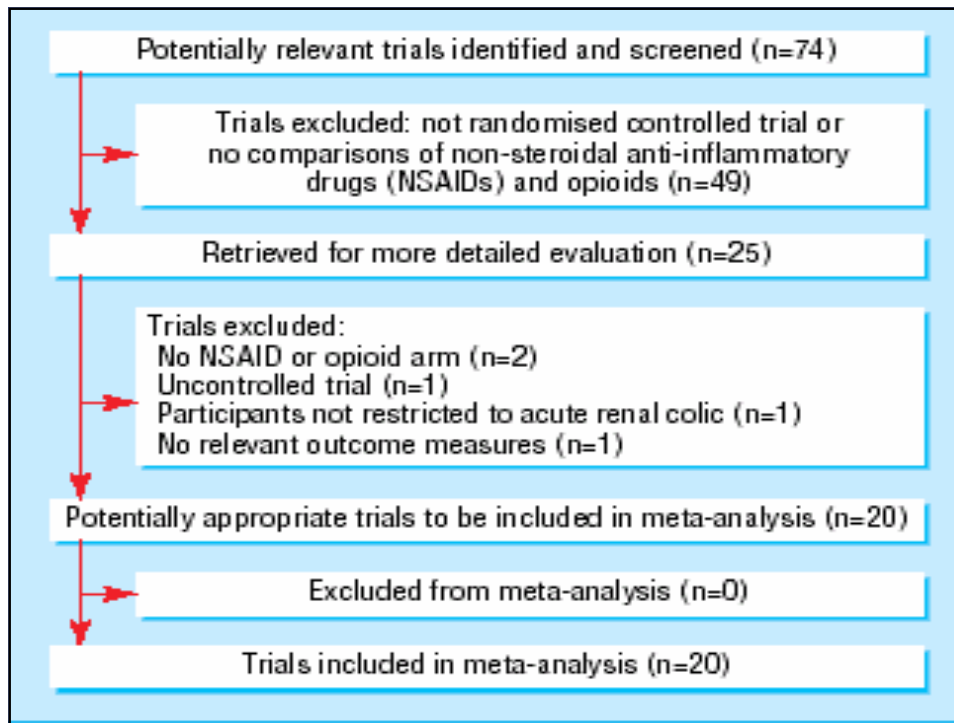
Objective To examine the relative benefits and disadvantages of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids for the management of acute renal colic.

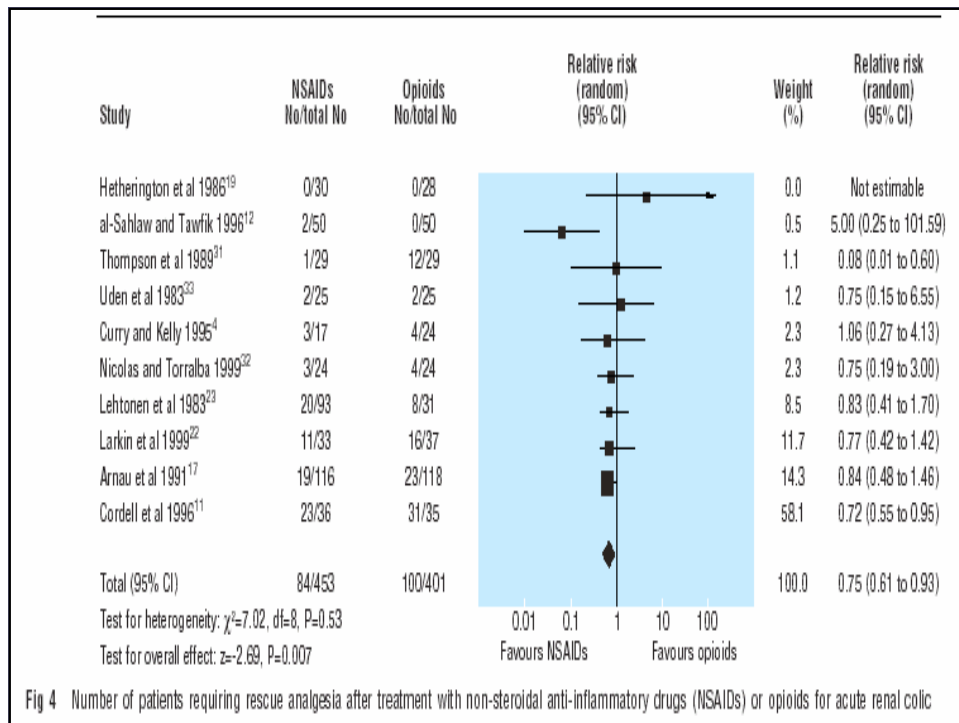
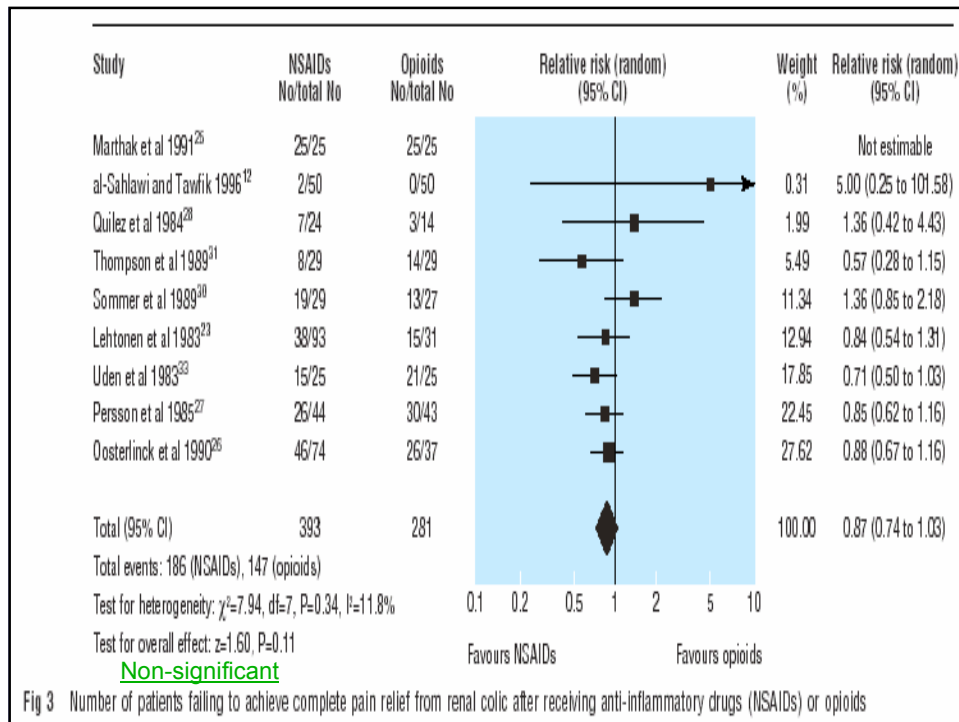
Data sources Cochrane Renal Group's specialised register, Cochrane central register of controlled trials, Medline, Embase, and reference lists of retrieved articles.

Review methods Randomised controlled trials comparing any opioid with any NSAID in acute renal colic if they reported any of the following outcomes: patient rated pain, time to pain relief, need for rescue analgesia, rate of recurrence of pain, and adverse events.

Methods

- 20 articles reviewed of 74 potential sources
- 1613 pts
- 5 different NSAIDS and 7 opioids
- 17 of 20 used IV or IM NSAIDS





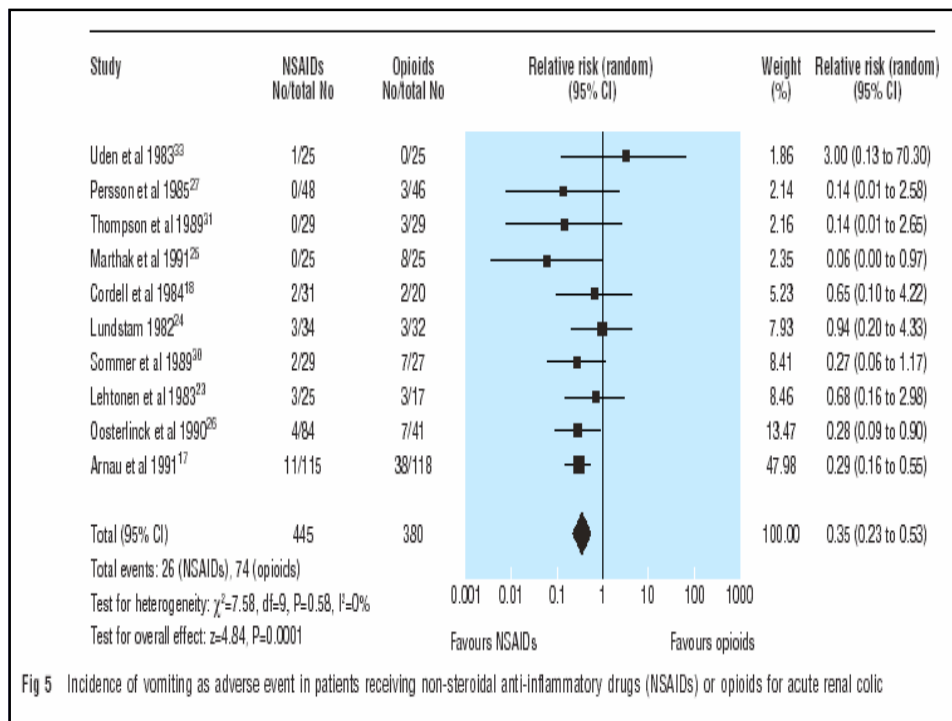


Fig 5 Incidence of vomiting as adverse event in patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) or opioids for acute renal colic

What is already known on this topic

Both non-steroidal anti-inflammatory drugs (NSAIDs) and opioids provide analgesia in acute renal colic

NSAIDs have well recognised side effects

What this study adds

NSAIDs achieve slightly greater reductions in pain scores than opioids in patients with renal colic

Patients with renal colic are less likely to need rescue analgesia if treated with NSAIDs

Opioids, particularly pethidine, are associated with a higher rate of vomiting and other adverse effects

NSAIDS and OPIOIDS Summary

- Both provide pain relief in renal colic
- NSAIDS less likely to require supplemental analgesia
- NSAIDS a/w less nausea and vomiting
- Combination therapy initially may be better than either alone
- Ketorolac (IM/IV) used in most studies

Difficulties With Literature Interpretation

- Equivalent NSAID / Opioid doses?
- Ad hoc reporting of side effects, no long term f/u of side effects
- Opioids not titrated appropriately
- Lack of clear guidelines for rescue analgesia

Alternative Analgesics for Renal Colic

1. Hyoscyamine (Anaspaz)
2. Hyoscine (Buscopan)
3. DDAVP
4. TENS
5. Local active abdominal warming

Sublingual Hyoscyamine Sulfate in Combination With Ketorolac Tromethamine for Ureteral Colic: A Randomized, Double-Blind, Controlled Trial

FEBRUARY 2001 37:2 ANNALS OF EMERGENCY MEDICINE

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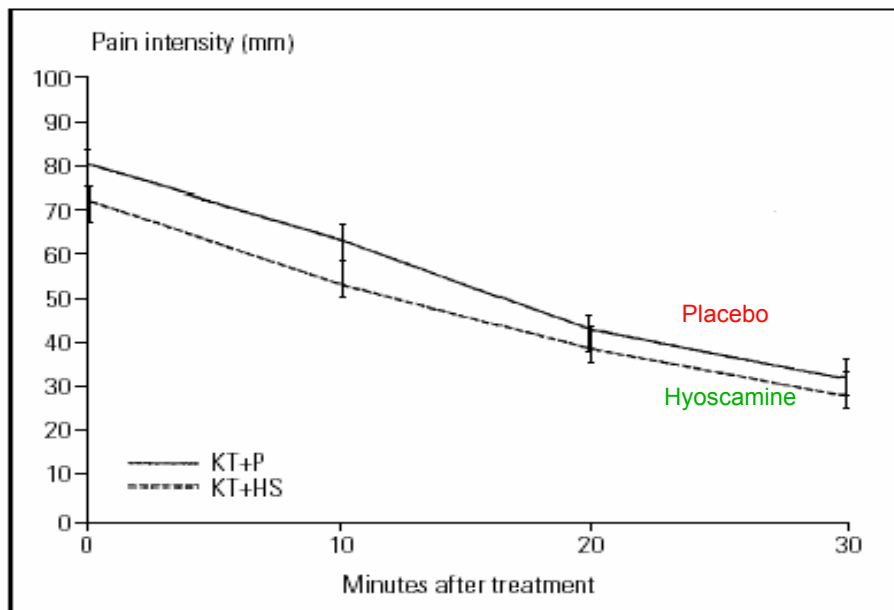
James B. Jones, MD, PharmD*
Beverly K. Giles, RN*
Edward J. Brizendine, MS†
William H. Cordell, MD*

Sublingual Hyoscyamine Sulfate in Combination
With Ketorolac Tromethamine for Ureteral Colic:
A Randomized, Double-Blind, Controlled Trial

Methods

- Prospective double blind RCT 2 centers
- Group 1: Ketorolac + hyoscamine
- Group 2: Ketorolac + placebo
- Rescue analgesia after 30 min PRN with meperidine
- Endpoint: Change in VAS at 30min

Figure 2.
Mean pain scores for HS+KT and KT+P over time.



Sublingual Hyoscyamine Sulfate in Combination
With Ketorolac Tromethamine for Ureteral Colic:
A Randomized, Double-Blind, Controlled Trial

Conclusions

- Both groups had significantly lower pain scores at 30 minutes than 0 minutes
- No difference between hyoscyamine and placebo
- Hyoscyamine has no benefit over placebo
- Lack of muscarinic receptors in ureter?

IS THERE A ROLE FOR ANTIMUSCARINICS IN RENAL COLIC?
A RANDOMIZED CONTROLLED TRIAL

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DOI: 10.1097/01.ju.0000165337.37317.4c

Purpose: We determined whether the addition of hyoscine butylbromide (Buscopan™) reduces the amount of opioid analgesia required and the need for ongoing opioid analgesia in acute renal colic.

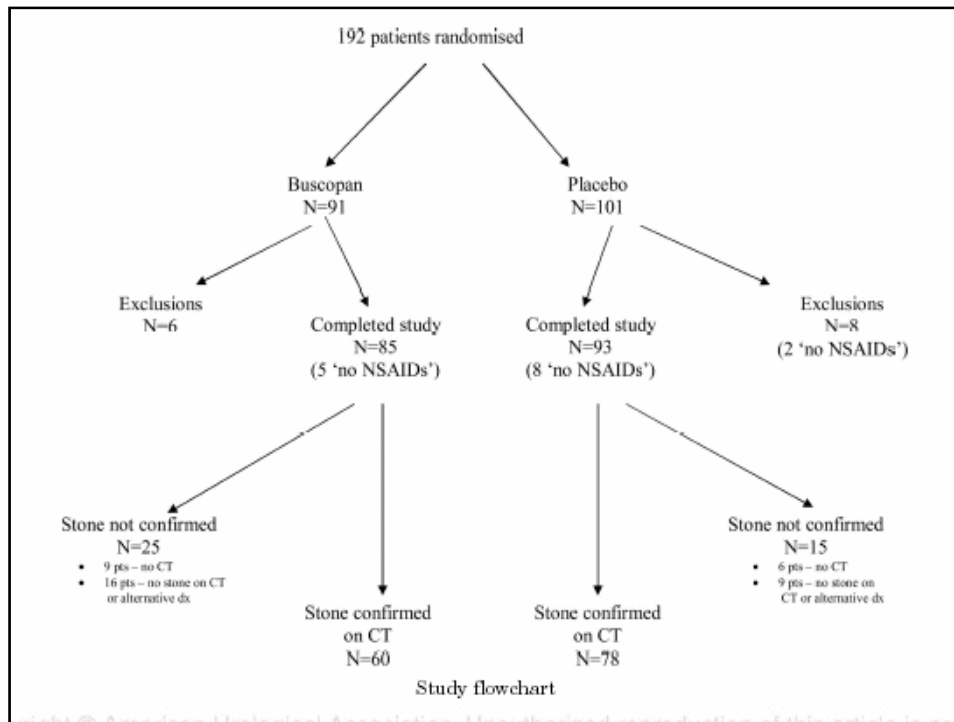


TABLE 2. *Main outcomes of intent to treat analysis*

	Buscopan	Placebo	p Value
Median mg/kg morphine (mean)	0.12 (0.13)	0.11 (0.12)	0.4*
No. further morphine required (%)	28 (33)	35 (38)	0.5†
No. admitted to hospital (%)	12 (14)	18 (19)	0.3†
No. adverse events (%)	15 (18)	17 (18)	0.9†

* Mann-Whitney U test.

† Chi-square test.

Conclusions: There is no evidence that Buscopan™ reduces opioid requirements or the need for ongoing opioid analgesia in acute renal colic.

An assessment of the clinical efficacy of intranasal desmopressin spray in the treatment of renal colic

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Objectives To assess the efficacy of desmopressin nasal spray compared with diclofenac given intramuscularly in patients with acute renal colic caused by urolithiasis.

Patients and methods The study included 61 patients randomized into three different groups; group A received desmopressin (40 µg, nasal spray), group B diclofenac (75 mg) intramuscularly and group C, both desmopressin and diclofenac. Pain was assessed using a visual analogue scale (a 10-cm horizontal scale ranging from 'no pain' to 'unbearable pain') at baseline, 10, 20 and 30 min after administering the treatments.

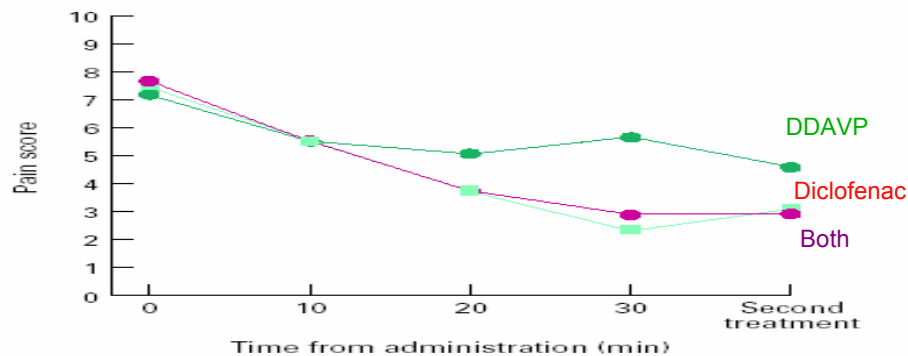


Fig. 1. The change in mean pain scores in the three groups (A, green; B, red; C, light green) with time after administration of therapy.

DDAVP: Conclusions

- Easy administration
- Minimal side effects
- Effective as single agent or combined
- Decreases need for second intervention
- Combined therapy more effective
- NO PLACEBO

Transcutaneous Electrical Nerve Stimulation: An Effective Treatment for Pain Caused by Renal Colic in Emergency Care

Bruno Mora,* Elisabetta Giorni, Michael Dobrovits, Renate Barker, Thomas Lang, Carmen Gore and Alexander Kober

From the Departments of Anesthesia and Intensive Care (BM, RB, TL, AK) and Urology (MD), University of Vienna, Vienna, Austria, and Departments of Anesthesia and Intensive Care, University "Tor Vergata" (EG), Rome, Italy, and University of Bucharest (CG), Bucharest, Romania

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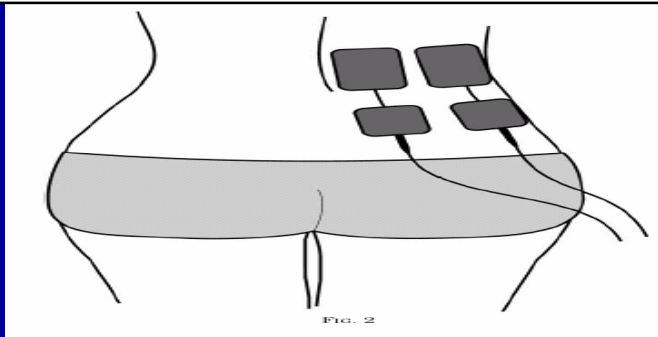
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DOI:10.1016/S0022-5347(05)00980-8

Methods

- 73 patients – performed by paramedics during transfer
- 1 paramedic places TENS, another monitors (Blinding)
- Group 1: TENS
- Group 2: Sham TENS
- VAS at entrance to ambulance and arrival at hospital



- Group 1:
 - Pain VAS from 86mm to 33mm
 - Anxiety VAS from 69mm to 38mm
- Group 2:
 - Pain VAS from 86mm to 83mm
 - Anxiety VAS from 72mm to 75mm

Transcutaneous Electrical Nerve Stimulation: An Effective Treatment for Pain Caused by Renal Colic in Emergency Care

Conclusions

- Effective pain and anxiety relief
- Useful in certain clinical settings

LOCAL ACTIVE WARMING: AN EFFECTIVE TREATMENT FOR PAIN, ANXIETY AND NAUSEA CAUSED BY RENAL COLIC

ALEXANDER KOBER, MICHAEL DOBROVITS, BOB DJAVAN, MICHAEL MARBERGER,
RENATE BARKER, PETRA BERTALANFFY, THOMAS SCHECK, BURKHARD GUSTORFF
AND KLAUS HOERAUF

From the Departments of Anesthesia and Intensive Care (AK, RB, PB, TS, BG, KH) and Urology (MD, BD, MM), Vienna General Hospital, University of Vienna, Vienna, Austria

- Group 1: Carbon fiber heating blanket at 42 C
- Group 2: Carbon fiber heating blanket passive
- VAS at entrance to ambulance and arrival at hospital

- **Warming:** Pain 83mm to 36mm $p < 0.001$
- **Warming:** Anxiety 79mm to 31mm $p < 0.001$
- **Warming:** Nausea 86mm to 41mm $p < 0.001$
- Control: Pain 82mm to 81mm
- Control: Anxiety 80mm to 75mm
- Control: Nausea 79mm to 80mm

Conclusions: Local active warming is an effective and easy to learn pain treatment for patients with acute renal colic in emergency care.

Medical Expulsive Therapy (MET)

1. Spontaneous stone passage
2. AUA 1997 Guidelines
3. Calcium channel blockers
4. Alpha blockers

Factors Influencing Stone Passage

Stone Factors	Patient Factors
Size	Anatomy
Location	Renal function
Shape	

Factors Influencing Decision

Stone Factors	Patient Factors
Size	Anatomy (Solitary / Transplant)
Location	Symptoms
Stone burden	Infection
Composition	Level of obstruction
Impaction	Renal function
	Duration of obstruction
	Expectations

Table 1. Spontaneous passage of small ureteral stones

Source	Stone size as reported	Location as reported	Sample size	Percentage passed in time frame
Brown, 1985	<5 mm	Ureter	100	88% in 3 months 98% in 1 year
Ueno et al., 1977	1-5 mm width 1-5 mm length	Ureter Ureter	311 138	75% in 1 year 88% in 1 year
Morse and Resnick, 1991	1-5 mm 1-5 mm	Proximal ureter Middle ureter Distal ureter	65 25 267	22% in 300 days 60% in 300 days 71% in 300 days
Ohkawa et al., 1993	1-5 mm	Ureter	846	91% unspecified
Kinder et al., 1987	<5 mm	Upper 1/3 Middle 1/3 Lower 1/3 Vesico-ureteric junction	84 total	75% unspecified 100% unspecified 100% unspecified 94% unspecified
Sandegaard, 1956	<4 mm	Upper ureter	42	26% in 1 week 43% in 2 weeks 55% in 4 weeks 69% in 12 weeks 81% in 18 months
		Lower ureter	192	70% in 1 week 82% in 2 weeks 85% in 4 weeks 90% in 12 weeks 93% in 18 months

AUA Guidelines 1997

Table 2. Likelihood of Passage of Ureteral Stones.*

Size of Stone	Mean No. of Days Required to Pass Stone	Likelihood of Eventual Need for Intervention %
≤2 mm	8	3
3 mm	12	14
4–6 mm	22	50
>6 mm†	—	99

* Data were obtained from Hubner et al.²⁴ and Miller and Kane.²⁵

† A stone of this size is unlikely to be passed spontaneously.

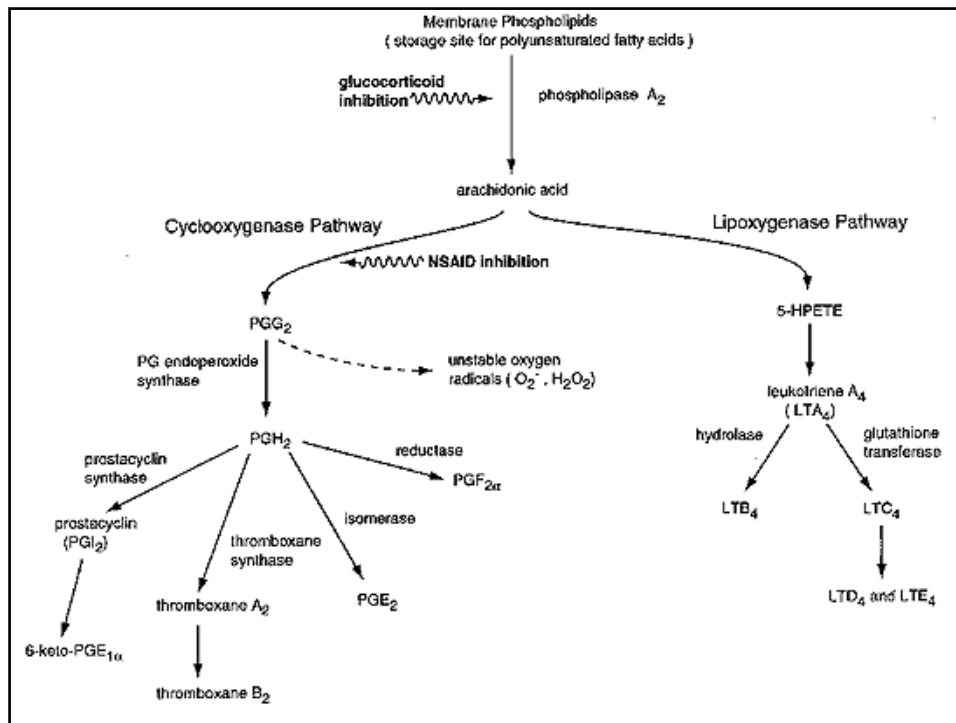
Teichman NEJM 2004

Corticosteroids

- Inhibit AA formation
- Reduce edema
- Multiple other effects
- Undesirable side effects

Corticosteroids: Cautions

- Peptic ulcer disease
- Diabetes
- Infections
- Mood disturbances



MET: Calcium Channel Blockers

Calcium Channel Blockers: MOA

- Ca levels \Rightarrow smooth muscle contraction
- Calcium ion influx inhibitor
- Decrease fast phasic contractions
- Slow phasic contractions intact
- Preserved peristalsis with decreased spasm
- Pain relief?
- Facilitate stone passage

CCB Dose

- Nifedipine 30-60mg PO OD

Nifedipine Contraindications

1. Pregnancy
2. Lactation
3. Previous hypersensitivity
4. Severe hypotension

INCREASING THE SUCCESS RATE OF MEDICAL THERAPY FOR EXPULSION OF DISTAL URETERAL STONES USING ADJUNCTIVE TREATMENT WITH CALCIUM CHANNEL BLOCKER

Skrekas T., Liapis D., Kalantzis A., Argyropoulos A., Doumas K., Lycourinas M.

General Hospital "G.Gennimatas", Urology, Athens, Greece

Eur Urol Supp 82:2 2003

INTRODUCTION & OBJECTIVES: The role of medical therapy facilitating the expulsion of distal ureteral stones is not well established. We evaluated the effectiveness of adjunctive treatment with a calcium channel blocker (nifedipine) in the management of distal ureteral stones.

MATERIAL & METHODS: 92 patients with radiopaque distal ureteral stones smaller than 1 cm were enrolled in a prospective study (lasted from April 2000 till May 2002). Diagnosis was established by means of KUB, ultrasonography and IVU. The patients were randomised in two groups. In group A, 46 patients (27 males, 19 females, median age 43 years old) received nimesulide 200mg /day plus nifedipine 30mg/day p.o. for 10 days. In group B, 46 patients (25 males, 21 females, median age 41,8 years old) received nimesulide only (200mg/day), for 10 days as well.

RESULTS: In group A the average stone size was 0,5 cm (0,3-0,8 cm) while in group B the average size was 0,55cm (0,3-0,9 cm). All patients were evaluated after 30 days with clinical examination, KUB and ultrasonography. At the endpoint 38 patients (83%) from group A were stone free with average expulsion time 6 days (range 2-12 days). 26 patients from group B (56%) were stone free with average expulsion time 18 days (14-23 days). A statistically significant difference was observed in both the stone free rate and expulsion time.

CONCLUSIONS: Adjunctive therapy with nifedipine could increase the success rate of distal ureteral stone (<1cm) conservative management.

INCREASING THE SUCCESS RATE OF MEDICAL THERAPY FOR EXPULSION OF DISTAL URETERAL STONES USING ADJUNCTIVE TREATMENT WITH CALCIUM CHANNEL BLOCKER

Skrekas et al, European Urology Supp 82 (2) 2003

Methods

- Nifedipine vs control (No steroids in either group)
- Group 1: Nifedipine 30mg/day for 10 days + NSAID
- Group 2: NSAID only
- KUB and US at 30 days

**INCREASING THE SUCCESS RATE OF MEDICAL THERAPY FOR
EXPULSION OF DISTAL URETERAL STONES USING ADJUNCTIVE
TREATMENT WITH CALCIUM CHANNEL BLOCKER**

Results

- Group 1 stone size 5mm
- Group 2 stone size 5.5mm
- Males = Females
- Group 1: 83% expulsion, 6 days
- Group 2: 56% expulsion, 18 days

**EFFECTIVENESS OF NIFEDIPINE AND DEFLAZACORT IN
THE MANAGEMENT OF DISTAL URETER STONES**

FRANCESCO PORPIGLIA, PAOLO DESTEFANIS, CRISTIAN FIORI, AND DARIO FONTANA

UROLOGY 36 (4), 2000

Objectives. To evaluate the effectiveness of medical therapy during watchful waiting in patients with distal ureter stones.

Methods. Ninety-six patients with radiopaque stones located in the distal tract of the ureter and with stone sizes of 1 cm or smaller were involved in the study. The patients were randomly divided into two groups. Group A (n = 48) received oral treatment with 30 mg of deflazacort daily (maximum 10 days) plus 30 mg of slow-release nifedipine daily (maximum 4 weeks). Group B (n = 48) underwent a wait-and-watch approach. Both groups of patients were allowed to use diclofenac on demand. Statistical analyses were carried out using Student's *t* test, the chi-square test, and Fisher's exact test.

EFFECTIVENESS OF NIFEDIPINE AND DEFLAZACORT IN THE MANAGEMENT OF DISTAL URETER STONES

FRANCESCO PORPIGLIA, PAOLO DESTEFANIS, CRISTIAN FIORI, AND DARIO FONTANA

Methods

- Nifedipine + Steroids vs No steroids control
- Distal ureter
- Stones <1cm
- Group 1: Nifedipine 30mg/day for 4 weeks + Steroid deflazacort 30mg/day 10 days
- Group 2: Control (no steroid)
- KUB + US weekly, urine straining
- IVP after 4 weeks

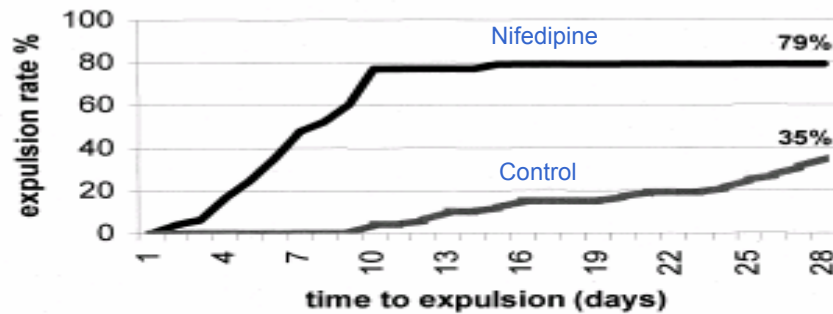


FIGURE 1. Expulsion rate and time to expulsion for treated (group A, black line) and untreated patients (group B, gray line).

- Average stone size 5.5mm and 5.8mm
- Stone expulsion 79% vs 35%
- Average expulsion time 7 days vs 20 days
- Diclofenac use 15mg vs 105mg

MET: Alpha Blockers

Ureteral Alpha Receptors

- Canine experiments (Morita et al Tohoku J Exp Med 1987)
- NE: Alpha > Beta receptor stimulation
- NE Ureteral Stimulation:
 - Increase peristaltic frequency
 - Elevated baseline pressure
 - Elevated contractile pressure
 - Decreased bolus volume
 - Decreased rate fluid transport
- Phenyphrine and clonidine – same effects as NE

Morita et al, Tohoku J Exp Med 1987

Ureteral Alpha Receptors

- Phentolamine (non-selective) and Prazosin (Alpha1)
 - Decreased peristaltic frequency
 - Fall in baseline and contractile pressure
 - Increase in rate of fluid transport
- Yohimbine (Alpha 2 antagonist)
 - decreased peristalsis and bolus formation
- Both alpha 1(phenylephrine) and alpha2 (clonidine-agonist) receptors in ureter

Tohoku J Exp Med 1987

Ureteral Alpha Receptors

- Heterogenous distribution of alpha receptors
- Distal ureter > Middle and Proximal
- Middle = Proximal
- All alpha subtypes
- Predominantly Alpha 1d > Alpha 1a

Sigala et al, Neurourology and Urodynamics 2005 24(2) 142-8

Ureteral Alpha Receptors

- Alpha 1d in intramural ureter / distal ureter and bladder
- Alpha 1a in prostate, urethra and bladder outlet + ureter
- Alpha 1b vascular smooth muscle

Tamsulosin/Flomax: MOA

- Alpha 1a/1d antagonist
 1. Decreases peristaltic frequency
 2. Decreases baseline pressure
 3. Decreases contractile pressure
 4. Increases bolus volume
 5. Increases fluid transport
 6. Increase pressure gradient around stone

Tamsulosin: Dose

- 0.4mg PO OD

Tamsulosin Contraindications

- Known hypersensitivity

Tamsulosin: Side Effects

- Dizziness
- Rhinitis
- Retrograde ejaculation

TABLE 1. Summary of all randomized prospective studies evaluating efficacy of medical expulsion therapy (outcomes favor medical expulsion therapy)

Medication (No. pts)	Mean (\pm SD) Stone Size (mm)	% Stone Passage	Mean Days to Passage	Stone Location
Borghi et al. ⁵				Majority distal ureter
Nifedipine + steroid (43)	6.7 (\pm 3.0)	87*	11.2*	
Placebo + steroid (43)	6.8 (\pm 2.9)	65	16.4	
Porpiglia et al. ⁷				Distal ureter
Nifedipine + steroid (48)	5.8 (\pm 1.8)	79*	7*	
Control (48)	5.5 (\pm 1.4)	35	20	
Cooper et al. ⁸				Distal ureter >50%
Nifedipine + steroid (35)	3.86	86*	12.6	
Control (35)	3.91	56	11.1	
Cervenakov et al. ¹⁰				Distal ureter
Tamsulosin (51)	Not reported	80*	Not available	
Control (51)	Not reported	63	Not available	
Dellabella et al. ¹¹				Juxtavesical ureter
Tamsulosin + steroid (30)	6.7	100*	2.73*	
Anticholinergic + steroid (30)	5.8	70	4.63	
Porpiglia et al. ¹³				Distal ureter
Tamsulosin + steroid (30)	5.4	85*	7.7*	
Nifedipine + steroid (30)	4.7	80	9.3	
Control (30)	5.35	43	12	
Yilmaz et al. ¹²				Distal ureter
Tamsulosin (29)	6.00 (\pm 1.25)	79*	6.3*	
Terazosin (28)	5.96 (\pm 0.83)	78*	5.7*	
Doxazosin (29)	5.93 (\pm 0.88)	75*	5.9*	
Control (28)	6.07 (\pm 1.41)	54	10.5	
Dellabella et al. ¹⁴				Distal ureter
Tamsulosin + steroid (70)	7.2 (\pm 2.4)	97*	3*	
Nifedipine + steroid (70)	6.2 (\pm 1.5)	77	5	
Phloroglucinol + steroid (70)	6.2 (\pm 1.7)	64	5	

* Statistically significant compared to control arm.

AUAUS 2006 Lesson 18

THE COMPARISON AND EFFICACY OF 3 DIFFERENT α 1-ADRENERGIC BLOCKERS FOR DISTAL URETERAL STONES

ERDAL YILMAZ,* ERTAN BATISLAM, MEHMED MURAD BASAR, DEVRIM TUGLU,
MEHMET FERHAT AND HALIL BASAR

From the Department of Urology, University of Kirikkale, Faculty of Medicine, Kirikkale, Turkey

TABLE 1. Demographic data of the 4 groups

	Group 1	Group 2	Group 3	Group 4
No.	28	29	28	29
Mean age \pm SD	41.60 \pm 12.01	40.62 \pm 10.27	41.67 \pm 11.41	42.13 \pm 10.46
Sex (M/F)	19/9	9/20	9/19	9/20
Mean cm ht \pm SD	168.07 \pm 5.84	168.82 \pm 5.90	169.14 \pm 6.07	168.79 \pm 6.20
Mean kg wt \pm SD	71.39 \pm 6.36	71.65 \pm 8.37	70.57 \pm 6.47	73.41 \pm 9.04
Mean cm stone size \pm SD	6.97 \pm 1.41	6.00 \pm 1.25	5.96 \pm 0.83	5.93 \pm 0.88
Stone localization (rt/lt)	13/15	16/13	14/14	14/15
	Control	Flomax 0.4mg	Terazosin 5mg	Doxazosin 4mg

THE COMPARISON AND EFFICACY OF 3 DIFFERENT α 1-ADRENERGIC BLOCKERS FOR DISTAL URETERAL STONES

ERDAL YILMAZ,* ERTAN BATISLAM, MEHMED MURAD BASAR, DEVRIM TUGLU,
MEHMET FERHAT AND HALIL BASAR

Methods

- Alpha blocker(No steroid) vs Control(No steroid)
- Comparison of different alpha blockers
- Distal stones (Juxtavesical or UVJ)
- Followed for up to 30 days
- KUB + US q weekly
- Strained urine

THE COMPARISON AND EFFICACY OF 3 DIFFERENT α 1-ADRENERGIC BLOCKERS FOR DISTAL URETERAL STONES

ERDAL YILMAZ,* ERTAN BATISLAM, MEHMED MURAD BASAR, DEVRIM TUGLU, MEHMET FERHAT AND HALIL BASAR

	Control	Flomax	Hytrin	Cardura
Expulsion%	54%	79%	79%	76%
Time (days)	10.5	6.3	5.8	5.9

THE COMPARISON AND EFFICACY OF 3 DIFFERENT α 1-ADRENERGIC BLOCKERS FOR DISTAL URETERAL STONES

ERDAL YILMAZ,* ERTAN BATISLAM, MEHMED MURAD BASAR, DEVRIM TUGLU, MEHMET FERHAT AND HALIL BASAR

2012

α 1-BLOCKER FOR DISTAL URETERAL STONES

TABLE 2. Results of randomization

	Group 1	Group 2	Group 3	Group 4
Stone expulsion rate	15/28 (53.57)	23/29 (79.31)	22/28 (78.57)	22/29 (75.86)
Mean days to expulsion \pm SD	10.54 \pm 2.12	6.31 \pm 0.88	5.75 \pm 0.88	5.93 \pm 0.59
Mean pain episodes \pm SD	2.42 \pm 1.39	1.72 \pm 0.88	1.57 \pm 0.23	1.67 \pm 0.17
Mean mg analgesic requirement \pm SD	182.14 \pm 19.83	129.31 \pm 17.81	117.85 \pm 17.85	118.68 \pm 16.21

THE COMPARISON AND EFFICACY OF 3 DIFFERENT α 1-ADRENERGIC
BLOCKERS FOR DISTAL URETERAL STONES

ERDAL YILMAZ,* ERTAN BATISLAM, MEHMED MURAD BASAR, DEVRIM TUGLU,
MEHMET FERHAT AND HALIL BASAR

Conclusions

- No steroids in any group in this study
- No difference between alpha blockers for pain, expulsion rates, or time to passage
- All alpha blocker groups have statistically significant differences from control for
 - expulsion rate
 - time to expulsion
 - analgesic usage

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NIFEDIPINE VERSUS TAMSULOSIN FOR THE MANAGEMENT OF
LOWER URETERAL STONES

FRANCESCO PORPIGLIA,* GIANPAOLO GHIGNONE, CRISTIAN FIORI, DARIO FONTANA
AND ROBERTO MARIO SCARPA

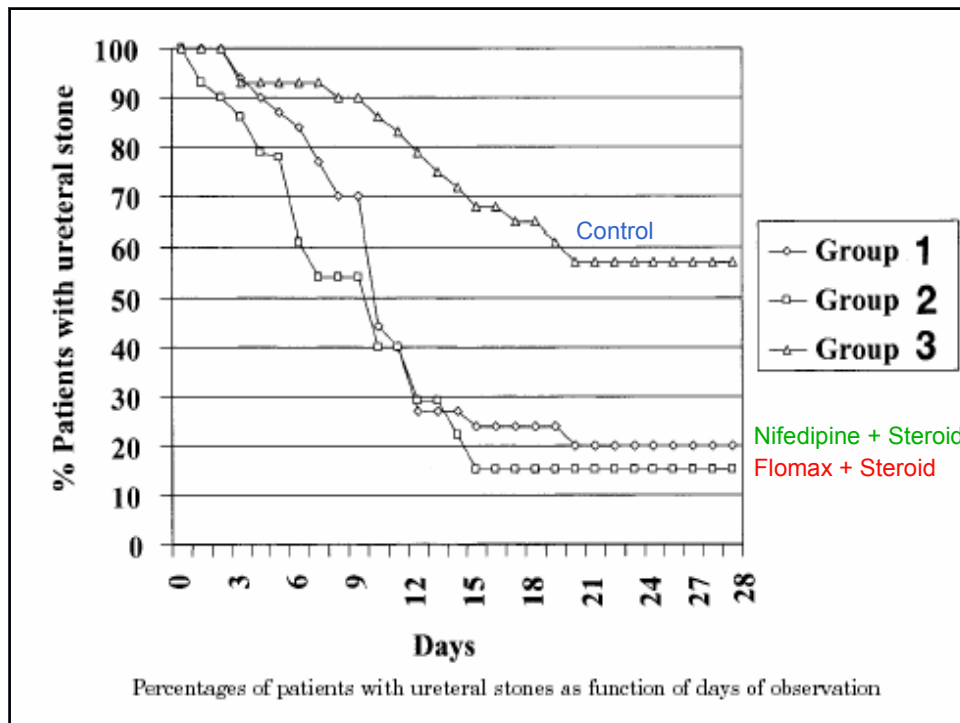
From the Division of Urology, Department of Clinical and Biological Sciences, University of Turin, "San Luigi" Hospital and Division of Urology, University of Turin, "San Giovanni Battista" Hospital (DF), Orbassano (Turin), Italy

Methods

- Group 1: Steroid (Deflazocort) + Nifedipine
- Group 2: Steroid (Deflazocort) + Flomax
- Group 3: Control (No steroids)
- Tests Flomax + Steroid vs No steroid

Methods

- Distal ureter (juxtavesical or UVJ)
- Steroid for 10 days
- Nifedipine or flomax for 28 days
- US and KUB weekly
- Filtered urine



	Nifedipine	Flomax	Control
Size	4.7	5.4	5.3
Expulsion	80%	85%	43%
Time	9.3	7.9	12
Diclofenac	19.5mg	26mg	105mg

Conclusions

- Size of stone only a factor for passage in control group
- No difference between men or women
- No difference between left or right
- No relation to stone size and time to passage
- No difference in any category between flomax or nifedipine

MEDICAL-EXPULSIVE THERAPY FOR DISTAL
URETEROLITHIASIS: RANDOMIZED PROSPECTIVE STUDY
ON ROLE OF CORTICOSTEROIDS USED IN COMBINATION
WITH TAMSULOSIN—SIMPLIFIED TREATMENT REGIMEN
AND HEALTH-RELATED QUALITY OF LIFE

MARCO DELLABELLA, GIULIO MILANESE, and GIOVANNI MUZZONIGRO

ABSTRACT

Objectives. To assess the clinical efficacy of the addition of a corticosteroid drug to tamsulosin in the medical-expulsive therapy of distal ureterolithiasis.

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MEDICAL-EXPULSIVE THERAPY FOR DISTAL
URETEROLITHIASIS: RANDOMIZED PROSPECTIVE STUDY
ON ROLE OF CORTICOSTEROIDS USED IN COMBINATION
WITH TAMSULOSIN—SIMPLIFIED TREATMENT REGIMEN
AND HEALTH-RELATED QUALITY OF LIFE

MARCO DELLABELLA, GIULIO MILANESE, and GIOVANNI MUZZONIGRO

Methods

- Efficacy of corticosteroids with tamsulosin in MET
- Group 1: Flomax
- Group 2: Steroids + Flomax
- 28 days
- Distal stones
- US weekly
- KUB days 10 and 28

TABLE I. Patient characteristics

Characteristic	Group 1 (n = 30)	Group 2 (n = 30)	P Value
Age			0.446
Mean	43.2	45.8	
SD	13.3	14.8	
Sex (n)			0.567
Male	20	23	
Female	10	7	
Stone lateral location (n)			0.785
Right	21	19	
Left	9	11	
Stone size (mm)			0.609
Median	6.4	6.9	
IQR	5–8	5.5–7.8	
Expulsion rate (%)			<u>0.612</u>
No. of patients	27	29	
Time to expulsion (hr)			<u>0.036</u>
Median	120	72	
IQR	72–168	24–120	
ER visits (%)	6.7 (2)	3.3 (1)	0.554
Urgent hospitalization (%)	0	0	—
Delayed hospitalization (%)	10 (3)	3.3 (1)	0.612
Analgesic use (vials)			0.625
Median	0	0	
IQR	0–1	0–0	
Workdays lost			0.994
Median	2	2	
IQR	1–3	1–3	
Drug side effects (%)	0	6.7 (2)	0.492

*Key: IQR = interquartile range; ER = emergency room.
Data in parentheses are number of patients.*

MEDICAL-EXPULSIVE THERAPY FOR DISTAL
URETEROLITHIASIS: RANDOMIZED PROSPECTIVE STUDY
ON ROLE OF CORTICOSTEROIDS USED IN COMBINATION
WITH TAMUSOLISIN—SIMPLIFIED TREATMENT REGIMEN
AND HEALTH-RELATED QUALITY OF LIFE

MARCO DELLABELLA, GIULIO MILANESE, and GIOVANNI MUZZONIGRO

Conclusions:

- No difference in expulsion rates between flomax + steroids vs flomax
- Steroids group had decreased time to expulsion (120hrs vs 72 hrs)
- Flomax very effective with or without steroids for distal stones

Urolithiasis/Endourology

RANDOMIZED TRIAL OF THE EFFICACY OF TAMSULOSIN, NIFEDIPINE AND PHLOROGLUCINOL IN MEDICAL EXPULSIVE THERAPY FOR DISTAL URETERAL CALCULI

MARCO DELLABELLA,* GIULIO MILANESE AND GIOVANNI MUZZONIGRO

From the Department of Urology and Division of Urology, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I-G. M. Lancini-G. Salesi, Polytechnic University of the Marche Region, School of Medicine, Ancona, Italy

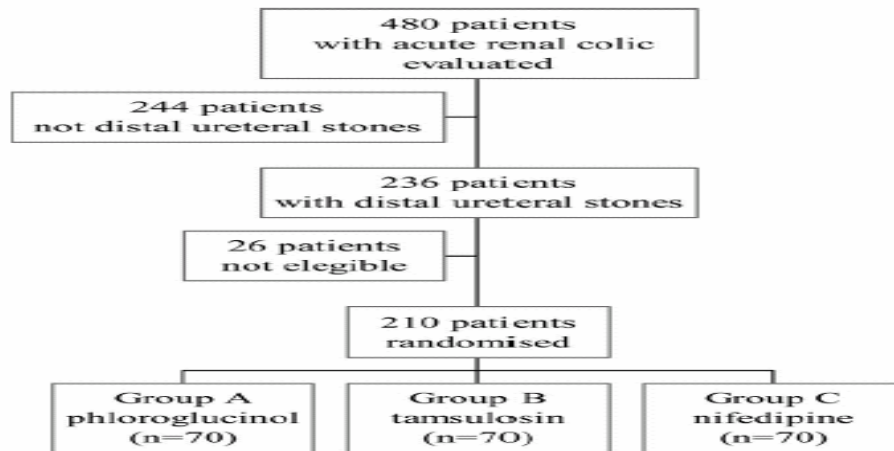


FIG. 1. Trial profile. All randomized patients completed trial

RANDOMIZED TRIAL OF THE EFFICACY OF TAMSULOSIN, NIFEDIPINE AND PHLOROGLUCINOL IN MEDICAL EXPULSIVE THERAPY FOR DISTAL URETERAL CALCULI

Methods

- All received cotrimazole, deflazacort, and PRN NSAIDS
- Distal stones (below iliacs)
- US q weekly
- KUB days 10 and 28
- Duration 28 days
- Urine straining

RANDOMIZED TRIAL OF THE EFFICACY OF TAMSULOSIN,
NIFEDIPINE AND PHLOROGLUCINOL IN MEDICAL EXPULSIVE
THERAPY FOR DISTAL URETERAL CALCULI

TABLE 1. *Baseline patient characteristics*

	Group 1	Group 2	Group 3	p Value
Mean age ± SD	39.8 ± 12.7	43.8 ± 13.9	41.8 ± 15.4	0.252
No. men/women	50/20	54/16	51/19	0.726
No. rt/lft stones	39/31	41/29	40/30	0.943
Stone size (mm):				
Mean (SD)	6.2 (1.7)	7.2 (2.4)	6.2 (1.5)	0.002
Median (range)	6 (4–11.8)	7 (4–18)	6 (4–11)	0.004
IQR	5–7	5.5–8	5–7	
Total of 70 patients per group.				

TABLE 2. *Randomization results*

	Group 1	Group 2	Group 3	p Value
No. expulsion (%)	45 (64.3)	68 (97.1)	54 (77.1)	≤0.0001
Time to expulsion (hrs):				
Median	120	72	120	≤0.0001
IQR	72–168	24–120	72–192	
No. hospitalization (%):				
Urgent	11 (15.7)	0	3 (4.3)	0.001
Delayed	13 (18.6)	1 (1.4)	11 (15.7)	0.004
Totals	24 (34.3)	1 (1.4)	14 (20)	≤0.0001
Total No. ureteroscopy (%)	22 (31.4)	1 (1.4)	14 (20)	≤0.0001
Analgesic use (No. vials):				
Median	2	0	1	≤0.0001
IQR	1–5	0–0	0–1	
No. workdays lost:				
Median	5	2	3	≤0.0001
IQR	2–6.25	1–2	1–5	
Total of 70 patients per group.	Phloroglucinol	Flomax	Nifedipine	

TABLE 3. Cox proportional hazards model multivariate analysis for factors predictive of stone expulsion

Variables	p Value	HR	95% CI
Age	0.545	1.004	0.992–1.016
Sex	0.202	0.796	0.561–1.130
Stone size	0.342	0.958	0.877–1.047
Stone lat location	0.195	0.811	0.596–1.111
Group 2 vs 1	0.0001	2.906	1.958–4.313
Group 2 vs 3	0.0001	2.548	1.741–3.728
Group 3 vs 1	0.517	1.141	0.766–1.698

- Only flomax + steroid group significantly better than other groups
- No control group – comparison study

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



European Association of Urology



Stone Disease

Corticosteroids and Tamsulosin in the Medical Expulsive Therapy for Symptomatic Distal Ureter Stones: Single Drug or Association?

Francesco Porpiglia *, Davide Vaccino, Michele Billia, Julien Renard, Cecilia Cracco, Gianpaolo Ghignone, Cesare Scoffone, Carlo Terrone, Roberto Mario Scarpa

Department of Urology, University of Turin, San Luigi Hospital, Orbassano (TO), Italy

Corticosteroids and Tamsulosin in the Medical Expulsive Therapy for Symptomatic Distal Ureter Stones: Single Drug or Association?

Methods

Parameter	Group A n = 30 (tamsulosin)	Group B n = 24 (deflazacort)	Group C n = 33 (tamsulosin + deflazacort)	Group D n = 24 (control group)	p value χ^2 test
Mean age, yr (range)	47.8 ± 1.3 (34-57)	45.3 ± 2.2 (40-55)	48.2 ± 0.6 (27-55)	45.2 ± 0.88 (33-50)	n.s.
Ureteral stone side (L/R)	14/16	10/14	15/18	9/15	n.s.
Male/female	17/16	20/4	23/10	12/12	-

n.s. = not significant.

Corticosteroids and Tamsulosin in the Medical Expulsive Therapy for Symptomatic Distal Ureter Stones: Single Drug or Association?

Methods

- Distal stones >5mm
- 10 days duration
- KUB , US +/- CT on day 11

Table 2 - Expulsion rates, analgesic consumption, and ureteroscopy

Parameter	Group A n = 30 (tamsulosin)	Group B n = 24 (deflazacort)	Group C n = 33 (tamsulosin + deflazacort)	Group D n = 24 (control group)	p value χ^2 test
Expulsion rate at 10 d	60% (18 of 30)	37.5% (9 of 24)	84.5% (28 of 33)	33.3% (8 of 24)	<0.001 (group C vs A, B, D)
Analgesic consumption, mg (range)	42.5 ± 0.4 (0-75)	50 ± 0.3 (0-150)	27.3 ± 0.5 (0-75)	81 ± 0.33 (75-225)	<0.001 (group C vs A, B, D)
Spontaneous expulsion rate while awaiting ureteroscopy	0%	0%	100% (5 of 5)	37.5% (6 of 16)	0.01 group C vs D
Ureteral stone side, L/R	8/10	5/4	15/18	3/3	n.s.
Overall expulsion	60% (18 of 30)	37.5% (9 of 24)	100% (33 of 33)	58.3% (14 of 24)	0.01 all groups except A vs D
Ureteroscopies	40% (12 of 30)	62.5% (15 of 24)	0%	42% (10 of 24)	0.01 all groups except A vs D
n.s. = not significant.					

Table 3 - Stone size

Parameter	Group A n = 30 (tamsulosin)	Group B n = 24 (deflazacort)	Group C n = 33 (tamsulosin + deflazacort)	Group D n = 24 (control group)	p
Average stone size, mm (range)	5.96 ± 0.33 (5-7)	5.83 ± 0.4 (5-8)	5.88 ± 0.23 (5-7)	5.71 ± 0.5 (6-7)	n.s.
Average stone size eliminated at 10 d, mm (range)	5.3 ± 0.2 (5-6)	5.7 ± 0.41 (5-7)	5.2 ± 0.33 (5-6)	5.5 ± 0.13 (5-6)	n.s.
Average stone size for ureteroscopy, mm	6.2 ± 0.9 (6-7)	5.74 ± 0.75 (5.5-6.3)	-	6.4 ± 0.55 (5.8-6.7)	n.s.
Average stone size waiting ureteroscopy, mm (range)	-	-	5.4 ± 1.2 (6-7)	6.6 ± 2.2 (6-7)	n.s.
n.s. = not significant.					

Corticosteroids and Tamsulosin in the Medical Expulsive Therapy for Symptomatic Distal Ureter Stones: Single Drug or Association?

Conclusions

- Evaluates the role of steroid vs control
- No difference between control and steroid group for expulsion rates
- No difference between flomax alone and control for expulsion rates
- Flomax and steroid most effective
- Flomax and steroid used significantly less analgesic than other groups and control

Medical therapy to facilitate urinary stone passage: a meta-analysis

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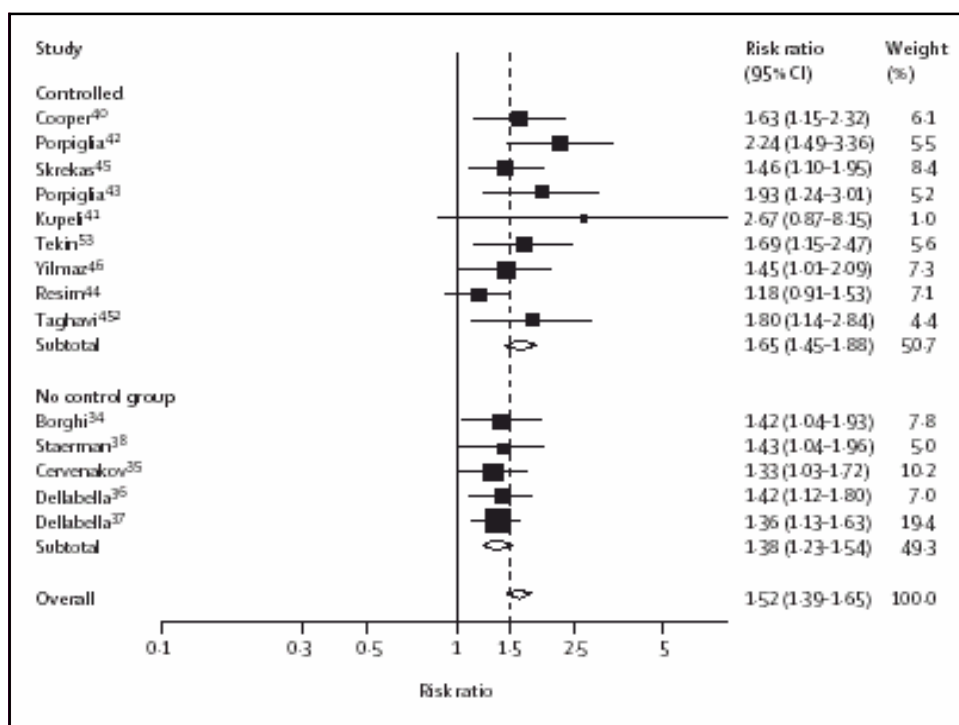
Methods

- Identify and summarize all RCT's using CCB and Alpha Blockers as MET
- MEDLINE, Pre-MEDLINE, CINAHL, and EMBASE
- 9 trials pooled (n=693)
- Primary endpoint was % expulsion
- Intent to treat (ie dropouts failed to pass stones)

Study	Year	Location	Number randomised	Number completed	Mean age (years, SD)*	% female*	Mean stone size (mm, SD)*
Cooper ²⁰	2000	Grand Rapids, MI USA	Total 76	Treatment 35 Control 35	For patients who completed the study: Treatment 45.4 Control 46.4	For those who completed the study: Treatment 17% Control 34%	For those who completed the study: Treatment 3.86 Control 3.91
Popiglia ²¹	2000	Turin, Italy	Treatment 48 Control 48	Treatment 46 Control 46	Treatment 44 Control 49	Treatment 46% Control 50%	Treatment 5.8 (1.8) Control 5.5 (1.4)
Skrekas ⁴	2003	Athens, Greece	Treatment 46 Control 46	Treatment 46 Control 46	Median age: Treatment 43.0 Control 41.8	Treatment 41% Control 46%	Treatment 5.0 Control 5.5
Popiglia ²¹	2004	Turin, Italy	Treatment 130 Treatment 228 Control 28	Treatment 129 Treatment 227 Control 28	Treatment 145.6 (12) Treatment 250.5 (17) Control 42.7 (16)	Treatment 137% Treatment 236% Control 43%	Treatment 14.70 (1.47) Treatment 25.42 (1.54) Control 5.35 (1.49)
Kupeli ²²	2004	Ankara, Turkey	Treatment 15 Control 15	Treatment 15 Control 15	Treatment 41.90 Control 43.74	n/a	Treatment 4.7 Control 4.9
Tekin ²³	2004	Istanbul, Turkey	Treatment 36 Control 39	Treatment 36 Control 39	Treatment 44 Control 42	n/a	Treatment 7.3 Control 6.8
Taghani ²⁴	2005	Mashhad, Iran	Treatment 120 Treatment 220 Control 24	Treatment 120 Treatment 220 Control 24	Overall 38	Overall 45%	n/a
Yilmaz ²⁵	2005	Kirkale, Turkey	Treatment 129 Treatment 228 Treatment 329 Control 28	Treatment 129 Treatment 228 Treatment 329 Control 28	Treatment 140.62 (10.27) Treatment 241.67 (11.41) Treatment 342.13 (10.46) Control 41.60 (12.01)	Treatment 169% Treatment 268% Treatment 369% Control 32%	Treatment 16.00 (1.25) Treatment 25.96 (0.83) Treatment 35.93 (0.88) Control 6.07 (1.41)
Resim ²⁶	2005	Kahramanmaraş, Turkey	Treatment 30 Control 30	Treatment 30 Control 30	Treatment 35.3 (10.9) Control 33.5 (9.7)	Treatment 27% Control 23%	Treatment 7.8 (2.3) Control 7.8 (2.2)

Data are number (SD) unless otherwise indicated. All studies took place in outpatient settings. n/a=data not available. *Values are for the starting population unless indicated otherwise.

Table 1: Study and patient summary characteristics



	Percentage of patients who passed their stones		Risk ratio (95% CI)
	Treatment	Control	
α blockers			
α blockers vs control			
Kopel ⁴¹	53% (8)	20% (3)	2.67 (0.87-8.15)
Tekin ⁵³	77% (28)	46% (18)	1.69 (1.15-2.47)
Yilmaz ⁴⁶	78% (67)	54% (15)	1.45 (1.01-2.09)
Resim ⁴⁴	87% (26)	73% (22)	1.18 (0.91-1.53)
Taghavi ⁴⁵	90% (18)	46% (11)	1.96 (1.24-3.11)
α blockers+steroids vs control			
Popiglia ⁴²	85% (24)	43% (12)	2.00 (1.27-3.15)
α blockers+steroids vs steroids			
Dellabella ³⁶	100% (30)	70% (21)	1.43 (1.13-1.81)
Dellabella ³⁷	97% (68)	64% (45)	1.51 (1.26-1.81)
α blockers+diazepam vs diazepam			
Červenáková ³⁵	80% (41)	60% (32)	1.33 (1.03-1.72)

Calcium-channel blockers				
Calcium-channel blockers vs control				
	Skrekas ⁸	83% (38)	56% (26)	1.46 (1.10-1.95)
	Taghavi ¹²	75% (15)	46% (11)	1.64 (0.99-2.71)
	Staerman ¹⁴ ‡	91% (21)	64% (16)	1.43 (1.04-1.96)
Calcium-channel blockers+steroids vs control				
	Cooper ¹⁰	82% (31)	50% (19)	1.63 (1.15-2.32)
	Popiglia ¹¹	79% (38)	35% (17)	2.24 (1.49-3.36)
	Popiglia ¹¹	80% (24)	43% (12)	1.87 (1.17-2.97)
Calcium-channel blockers+steroids vs steroids				
	Borghi ¹³	79% (34)	56% (24)	1.41 (1.04-1.93)
	Dellabella ¹⁷	77% (54)	64% (45)	1.20 (0.97-1.49)

α blockers vs calcium-channel blockers				
		α blockers	Calcium-channel blockers	
Without steroids				
	Taghavi ¹²	90% (18)	75% (15)	1.20 (0.90-1.61)
With steroids in each group				
	Popiglia ¹¹	85% (24)	80% (24)	1.07 (0.85-1.35)
	Dellabella ¹⁷	97% (68)	77% (54)	1.26 (1.10-1.44)

Lancet Review Conclusions

- MET with nifedipine or tamsulosin had 65% greater expulsion rate than control
- ARR 31%
- Small benefit with corticosteroids
- Definitive high quality RCT still required

MET Summary CCB's

- Most studies distal stones
- Effective as MET
- Reduction in analgesic usage
- Decreased time to passage
- Well tolerated
- Effective with or without steroids

MET Summary: Tamsulosin

- All studies distal stones
- Pharmacologically selective
- Effective as MET
- Decreases time to passage
- Well tolerated
- Effective with or without steroids



