



Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

M.E. is a 27 y/o woman with a h/o R ureteral stone (2mm, obstructing, at UVJ) in June 2011, UTI in July 2011 (treated as an outpatient with ciprofloxacin), now admitted with urinary frequency, urgency, suprapubic and bilateral flank pain, as well as R CVAT, with pyuria and likely pyelonephritis. CT abdomen/pelvis without contrast revealed 2.5mm and 1mm stones in the L kidney. She is being treated with IV ceftriaxone for her E. coli UTI. Despite IV morphine sulfate 1-4mg q3-8 hours PRN, she continues to report colicky pain. On hospital day 3 she denied any passage of a stone. It was suggested that she receive daily tamsulosin therapy.

Clinical Question: Does tamsulosin help decrease colicky pain and/or accelerate the passage of a stone in a patient with nephrolithiasis?

Background:

- Urinary stone disease
 - o affects 5-15% of the population in Europe and North America
 - o often located in the distal ureter
 - o spontaneous passage rates range from 71-98%, with average 8 days for stone <2mm, 12 days if <3mm
 - o factors affecting passage inc. stone size, location, shape; patient's anatomy, renal fxn
 - o in complete obstruction, renal injury can occur in 3-4 weeks (usual max wait time for spontaneous clearance)
- Characteristics of the ureter
 - o stone must travel 22-30cm
 - o inner longitudinal smooth muscle and outer circular smooth muscle → peristalsis
 - o high densities of α -1A and α -1D receptors in distal third, UVJ which mediate basal tone, peristaltic frequency, contractions
 - o sensory nerves: visceral afferents travel to ganglia → referred pain to subcostal, ilioinguinal, iliohypogastric, genitofemoral nerves
- Urinary stones cause pain
 - o Obstruction → distention of renal capsule, collecting system, ureter
 - o Mucosal irritation
 - o Reflex ureteral spasm → renal colic
- Current therapy for urinary stones
 - o Surgical
 - Extracorporeal shockwave lithotripsy (ESWL)
 - Ureteroscopic stone extraction
 - if stone is large enough
 - o Medical therapy - time, fluids, time, analgesia, time
 - o Medical expulsion therapy
 - calcium channel blockers (ie. nifedipine) as a way to enhance ureteral smooth muscle relaxation (as Ca mediates contraction)... but potential contraindications for patients with multiple medical problems
 - peripheral α -blockers are also being investigated, inc. doxazosin, terazosin (which were not that effective) as well as tamsulosin

- Tamsulosin (Flomax ®)
 - tamsulosin is a selective α -1A receptor antagonist with some α -1D receptor antagonism
 - main use is for symptoms of BPH
 - side effects include dizziness, hypotension, retrograde ejaculation, SJS, rhinitis, etc.
 - most research around tamsulosin is about adjunctive therapy after ESWL to assist stone clearance
 - a few poorly designed studies so before 2009 had negative findings about use of tamsulosin in medical therapy of stones
 - can tamsulosin be used as part of pure medical therapy for urinary stones?

Search Strategy

Database: PubMed

"tamsulosin"[Supplementary Concept] AND "Ureteral Calculi"[Mesh] NOT "Lithotripsy"[Mesh] AND "Randomized Controlled Trial"[Publication Type] → 28 results

Article chosen:

Al-Ansari A, et al. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. Urology 2010; 75:4-8.

Group	Criteria or definition	n
Population screened.	Patients presenting to the ED with acute flank pain	?
Inclusion criteria	Single radioopaque unilateral stone of ≤ 10 mm located below common iliac vessels as diagnosed on noncontrast CT; normal renal function; no UTI; no ESWL	100
Exclusion criteria	Age < 18 yrs; nonradioopaque stone; multiple stones; UTI; severe hydronephrosis; hypotension; pregnancy; peptic ulcer; history of ureteral surgery; those taking calcium-channel blockers; those refusing to participate	? – though noted to be 4% exclusion rate
Treatment group	0.4 mg tamsulosin PO daily	50
No treatment group	placebo	50

Primary endpoint: stone expulsion rate

Secondary endpoints: number of pain episodes; use of PRN diclofenac injections; time for passage of the stone

- Are the Results of the Trial Valid?
 - Randomized: Yes; 50 patients per arm were randomized
 - All patients accounted for at end: 4 patients in placebo group were lost to follow-up; 9 patients didn't pass the stone in tamsulosin group vs. 18 in placebo
 - Intention to treat:
 - Did not include patients lost to follow-up (4 in placebo group)
 - No patients dropped out due to side effects
 - None developed intractable pain, fever, severe hydronephrosis, inc in Cr > 2
 - Patients pursued other modes of therapy if pain was uncontrolled by diclofenac PRN, fever, inc in Cr > 2 mg/dL, or severe hydronephrosis
 - Blinding: double-blind – both investigators and patients
 - Groups similar at start of trial: statistically insignificant differences in demographics (study vs. control): middle-aged (37 vs. 36); male predominance (64% vs. 70%); R-sided stone (68% vs. 58%); stone size (5.88mm vs. 6.04mm); equal distribution $>$ or ≤ 5 mm

- Equal treatment of groups:
 - Followed with weekly KUB, U/S, U/A for 4 weeks or until passage of stone, whichever came first
 - PRN 75mg diclofenac injections
 - advised to drink minimum of 2L water daily
 - asked to strain urine
 - patients stopped taking pill when stone passed
- Did randomization work? Yes
- Powered at 80% with n=43 in each arm given prior data showing that expulsion is 90% and 65% with or without tamsulosin
- Are the Results of the Trial important?
 - Size of treatment effect: significant in primary and secondary endpoints
 - Precision of the estimate of the effect: small sample size, large standard deviations

Table 2. Overall results

	Tamsulosin (n = 50)	Placebo (n = 46)	P
Expulsion rate (n)	41/50 (82%)	28/46 (61%)	.02
Expulsion time (d), mean ± SD	6.4 ± 2.77	9.87 ± 5.4	.001
Pain episodes, mean ± SD	1.6 ± 1.3	2.3 ± 1.4	.02
Need for injection, mean ± SD	0.9 ± 0.93	1.8 ± 1.3	.001
Dose of injection (mg), mean ± SD	67.5 ± 69.8	127.2 ± 89.3	.001
Side effects (n)			
Retrograde ejaculation	1	0	
Dizziness	2	2	
Headache	2	2	
Rhinitis	1	0	
Fatigue	2	1	
Postural hypotension	1	0	
Total	9	5	

- Can I apply these results to my patient?
 - Comparison of my patient to trial patients: multiple stones; not a distal stone on this presentation; UTI
 - Size of stone mattered (but other variables didn't)
 - Expulsion rate in tamsulosin group: 96% for <5mm vs. 69% for >5mm (p=0.01)
 - Expulsion time for stones <5mm 6 (tamsulosin) vs. 10 days (control) and for stones >5mm 9 vs. 13 days (not significant?)
 - But not necessarily because of tamsulosin itself
 - All clinically important outcomes considered: stone clearance + pain experienced
 - Likely benefits outweigh potential harms and cost: cost of drug for up to 4wks vs. cost of pain meds, possible hospitalization, etc. – needs more investigation

References:

- Al-Ansari A, et al. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. *Urology*. 2010; 75:4-8.
- Arrabal-Martin M, et al. Treatment of ureteral lithiasis with tamsulosin: literature review and meta-analysis. *Urol Int*. 2010; 84(3): 254-9.
- Lipkin M and Shah O. The use of alpha-blockers for the treatment of nephrolithiasis. *Rev Urol*. 2006; 8 Suppl 4: S35-S42.
- Porena M et al. Pain killers and antibacterial therapy for kidney colic and stones. *Urol Int*. 2004; 72 Suppl 1: 34-9.
- Vincendeau S, et al. Tamsulosin hydrochloride vs. placebo for management of distal ureteral stones: a multicentric, randomized, double-blind trial. *Arch Int Med*. 2010 Dec 13; 170(22): 2021.
- Welk BK and Teichman JM. Pharmacological management of renal colic in the older patient. *Drugs Aging*. 2007; 24(11): 891-900.
- Zheng S, et al. Tamsulosin as adjunctive treatment after shockwave lithotripsy in patients with upper urinary tract stones: a systematic review and meta-analysis. *Scand J Urol Nephrol*. 2010 Dec; 44(6): 425-32.