Critical Review Form
Therapy

Randomized Trial of the Efficacy of Tamsulosin, Nifedipine and Phloroglucinol in Medical Expulsive Therapy for Distal Ureteral Calculi, *J Urology* 2005; 174:167-172

Objectives: **"To assess and compare the expulsive effects of orally administered phloroglucinol, tamsulosin, and nifedipine as MET (medical expulsive therapy) for distal ureteral calculi greater than 4mm in diameter when administered up to 28 days after the first painful manifestation." (p. 167-168).**

Methods: **Between May 2002 – July 2003, non-pregnant individuals over age 18 years without acute or chronic renal insufficiency, pre-existing α-antagonist/ β-blocker/ CCB/ nitrate therapy, fever, multiple stones, prior ureteral surgery or endoscopy, diabetes, peptic ulcer disease, or symptoms for more than 1-day were recruited from the ED of one Italian hospital when they were referred for renal colic to Urology. Kidney stones were confirmed by US (not CT!) and/or abdominal x-ray. Stones had to exceed 4 mm for inclusion.**

Randomization occurred via four Urologists and a random number table, although allocation concealment (to patients, treating physicians, nurses, family, or outcome assessors) is not described. All patients in every arm received cotrimoxazole (2 tablets daily for 8 days) and deflazacort (30 mg daily for 10 days). In addition, Group 1 received phloroglucinol (an anticholinergic agent), Group 2 tamsulosin (0.4 mg daily), and Group 3 slow-release nifedipine (1 tablet daily). Treatment continued for 28 days or until the stone was expelled. All patients also received self-administered intramuscular diclofenac as needed for home pain management and the number of vials used was tracked. All drugs supplied to patients were free. All patients were managed as outpatients.

Follow-up occurred in the Urology Clinic every seven days with ultrasound and creatinine measured. Plain abdominal x-ray was on days 10 and 28. The primary outcome was the proportion of stone expulsion medically as confirmed by abdominal x-ray and/or ultrasound. Secondary outcomes included quantity of analgesics used, need for hospitalization and/or endoscopic procedures, therapy side-effects, workdays lost, and quality of life (QOL).

Based upon power 80%, α =0.05, 30% projected difference in expulsion rates between Groups 1 and 2, and a 20% dropout rate, 70 subjects were required in each arm.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, via a random number table (p.168)
2.	Was randomization concealed (blinded)?	Not clearly stated, so probably not.
3.	Were patients analyzed in the groups to which they were randomized?	Endpoints were "analyzed on an intent-to-treat basis" (p.168)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Tamsulosin group had significantly larger stones (6.2 vs. 7.2mm) Table 1, but otherwise the groups did not differ in age, gender, or stone location.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Uncertain so possible bias.
2.	Were clinicians aware of group allocation?	Not clearly stated – probably yes thus introducing bias.
3.	Were outcome assessors aware of group allocation?	Not clearly stated – probably yes thus introducing bias.
4.	Was follow-up complete?	"No patient was lost to follow-up" (p.169)
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• Among 480 kidney stone patients encountered during the study period, 210 (44%) were eligible and enrolled. (Fig 1, p.168) • Stone expulsion occurred in 79.5% of the cohort including 64.3% phloroglucinol, 77.1% nifedipine, and 97.1% tamsulosin. This translates to NNT 5 (95%, CI 4-10) to successfully expel one stone with tamsulosin as opposed to nifedipine. • Tamsulosin also induced more rapid stone expulsion (72-hours vs. 120-hours in both other groups, $p \leq 0.0001$) and less missed workdays (2 vs. 3 in nifedipine group, NS). • No tamsulosin patients required any adjunctive analgesia or urgent hospitalizations. • No patient in any group had an increased Cr during follow-up. • For QOL, tamsulosin patients had better usual activity performance ($p=0.008$) and less pain ($p=0.015$) compared with nifedipine. Tamsulosin was superior to phloroglucinol by all QOL measures. • Although SE rates, features, and group breakdowns are not provided, "the frequency of side effects observed was not different among the 3 groups" (p.170).

		• There was no correlation between stone size and expulsion time in any patient. Furthermore, Cox proportional hazards model demonstrated that age, gender, stone size, and stone location were not independent predictors of stone expulsion (Table 3) (p.170). However, treatment with tamsulosin vs. nifedipine is an independent predictor of successful stone expulsion (HR 2.5, 95%, CI 1.7-3.7, p=0.0001).
2.	How precise was the estimate of the treatment effect?	CI is only provided for the HR and these are sufficiently narrow.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes - ED patients with confirmed kidney stones, although the large number of excluding conditions necessitate caution before applying to undifferentiated ED populations.
2.	Were all clinically important outcomes considered?	No – medication compliance was not assessed, but investigators did assess adverse events and quality of life.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes, tamsulosin is cheap, readily available, relatively safe and well-tolerated. If it can replace 1-month of suffering and be more available than the alternatives (ureteroscopy or lithotripsy) than patients will definitely benefit.

Limitations

1) **Single center study so limited external validity, but this study supports a growing body of evidence supporting α-antagonist as first-line MET.**

2) **Investigators did not report details of adverse drug effects**

3) **Did not exclude hypotension or other contraindications to α-antagonists or nifedipine. How low can BP reside before α-antagonist should be avoided?**

4) **Used concurrent steroid and antibiotic with all treatment arms. This is not standard of care and may have skewed results in all groups. Physicians treating kidney stone patients with stones > 4mm cannot confidently apply results without similarly using steroids and antibiotics, but are these necessary or would tamsulosin alone suffice?**

5) **No NNT or 95% CI are reported.**

6) **Patients and physicians were not blinded. Why?**

Bottom Line

Non-pregnant, non-diabetic, afebrile kidney stone patients without renal dysfunction presenting to one Italian ED with stone > 4mm and treated with NSAID analgesia, daily steroids, and antibiotics have significantly better (NNT = 5) and faster (2 days vs. 3 days) kidney stone expulsion with tamsulosin than with nifedipine. Phloroglucinol, an anticholinergic agent, is inferior to both nifedipine and tamsulosin and should not be used. Tamsulosin, a $\alpha_{1A} - \alpha_{1D}$ adrenergic antagonist is a ureteral smooth muscle relaxant which may also inhibit C-fiber or sympathetic post ganglionic pain transmission to the CNS and should be standard therapy for kidney stones > 4mm, if no contraindications exist.