CJEM Journal Club

Comparison of Tamsulosin, Nifedipine, and Placebo for Ureteric Colic

Reviewed by: Michael Gottlieb, MD*; Damali Nakitende, MD*

Clinical Question
Do calcium channel blockers or alpha blockers improve renal stone passage when compared with placebo?
Article Chosen
Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet* 2015;386 (9991):25-31, doi: 10.1016/S0140-6736(15)60933-3.

Keywords: medical expulsion therapy, nephrolithiasis, kidney stones, tamsulosin, nifedipine

OBJECTIVES OF THE META-ANALYSIS

The primary objective measured in this study was the proportion of patients presenting with ureteric colic who did not require intervention for stone clearance within four weeks of receiving tamsulosin, nifedipine, or placebo. Secondary outcomes included pain, time to stone passage, overall health status, and adverse events.

BACKGROUND

Urolithiasis and ureteric colic are common diagnoses in the emergency department. Approximately 12% of the population suffers from urolithiasis, with over two million outpatient visits related to the symptoms of these stones.[1] Medical expulsion therapy (MET) is commonly initiated in the emergency department (ED) for patients who present with uncomplicated ureteral stones in an attempt to facilitate passage and avoid more invasive procedures like extracorporeal shock wave lithotripsy and stent placement. MET involves the use of alpha-adrenergic receptor antagonists (commonly, tamsulosin) or calcium channel antagonists (commonly, nifedipine), which provide smooth muscle relaxation to the urinary tract, presumably facilitating passage of the calculi.[1-5] There have been multiple randomized trials assessing the use of MET, each with limitations, resulting in contradictory results. This has resulted in a call for larger and more rigorous studies of MET in ureteric colic.

METHODS

Population studied

This study enrolled adults aged 18-65 years presenting with ureteric colic with one ureteric stone of 10 mm or less (at the largest dimension) identified on CT scan. Patients with sepsis, an estimated glomerular filtration rate less than 30 mL per minute, requiring immediate intervention, and those already taking or unable to take an alpha blocker or calcium channel blocker were excluded from this trial.

Study design

This was a multi-centre, randomized, placebo-controlled trial that consecutively enrolled patients presenting to 24 United Kingdom National Health Service hospitals with ureteric colic. Patients were allocated to once daily oral tamsulosin 400 mcg, nifedipine 30 mg, or placebo in a 1:1:1 ratio by a remote randomization system, using an algorithm with study site, stone size (≤5 mm or >5 mm), and stone location (upper, middle, or lower ureter) as minimization

From the *Department of Emergency Medicine, Cook County (Stroger) Hospital, Chicago, IL, United States.

Correspondence to: Michael Gottlieb, MD, Department of Emergency Medicine, Cook County (Stroger) Hospital, 1900 W. Polk St., 10th Floor, Chicago, IL, 60612, United States; Email: michaelgottliebmd@gmail.com

 CJEM 2017;19(2):156-158 DOI 10.1017/cem.2015.105

covariates. Each participant received 28 identical-appearing capsules and took them until either spontaneous stone passage occurred, the decision for intervention was made, or four weeks had passed since randomization, whichever came first. Patients were followed up at four and 12 weeks.

Outcomes measured

The primary outcome measured in this study was spontaneous stone passage within four weeks, defined as the proportion of patients who did not require intervention for stone clearance within four weeks of randomization. Secondary outcomes included pain, assessed by participant-reported number of days of analgesic use and visual analog scale at four weeks, time to stone passage, health status assessed by the Short Form (SF)-36 questionnaires, and safety (assessed by participant report of discontinuation of medication due to adverse effects and by serious adverse events monitoring).

RESULTS

Between January 2011 and December 2013, 1,167 patients were randomly assigned (391 to tamsulosin, 387 to nifedipine, and 389 to placebo). Of these, 17 were subsequently excluded for ineligibility and 14 were lost to follow up, resulting in 1,136 patients (97%) being included in the primary outcome analysis. There were no significant differences in the baseline characteristics between treatment groups.

There was no significant difference in the primary outcome of spontaneous stone passage at four weeks among all three treatment arms. Tamsulosin resulted in no intervention in 81% of patients, compared with 80% in the nifedipine arm and 80% in the placebo arm (Table 1). These findings were consistent among pre-defined subgroups of sex, stone size (≤5 mm or >5 mm), and stone location (upper, middle, or lower ureter). No significant differences were noted in any of the secondary outcomes of days of analgesic use, pain visual analog scale, time to stone passage, or health status. Serious adverse events were rare and not significantly different between groups.

Table 1. Comparison of tamsulosin, nifedipine, and placebo for spontaneous stone passage.

Comparison Group	Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)
MET vs. placebo	1.04 (0.77-1.43)	0.8% (−4.1 to 5.7)
Tamsulosin vs. nifedipine	1.07 (0.74-1.53)	1.0% (−4.6 to 6.6)
Tamsulosin vs. placebo	1.08 (0.76-1.56)	1.2% (−4.4 to 6.9)
Nifedipine vs. placebo	1.02 (0.71-1.45)	0.2% (−5.4 to 5.9)

CI, confidence interval; MET, medical expulsive therapy

STUDY CONCLUSION

Tamsulosin 400 mcg and nifedipine 30 mg are not effective at decreasing the need for further treatment to achieve stone clearance in four weeks for patients with expectantly managed ureteric colic.

COMMENTARY

Many professional urologic societies recommend medical expulsive therapy (MET) with either alpha blockers or calcium channel blockers for urolithiasis based on an expectation of increased stone passage and improved pain control.[2,3] These recommendations arise from small studies with significant limitations, including small sample sizes, inadequate blinding, and selection of patient populations with predominately small ureteral stones. A recent Cochrane Review also supported the use of alpha blockers, but was limited by the same issues with the included studies.[4] This has resulted in a call for larger and more rigorous studies of MET in ureteric colic.

Pickard et al. conducted a well-designed study comparing two commonly prescribed types of MET with placebo for efficacy of stone passage.[6] Overall, they demonstrated no significant difference between MET and placebo for the primary outcome of stone passage at four weeks. It is important to note that lack of urologic intervention is an imprecise surrogate marker for evaluating the true efficacy of MET for stone passage, but does have significant value as a patient-oriented outcome. Alternatively, confirming stone passage with repeat imaging could have provided a more accurate assessment of true stone passage, but comes at the risk of significantly increased costs and radiation exposure.

Additionally, there were no significant differences in pain scales or number of days with pain medication. One must be cognizant that these were secondary

outcomes assessed with surveys, which were not adequately powered and suffered from significantly decreased follow-up rates when compared with the primary outcome (62% vs. 97%). Finally, it appears that this study was performed in a routine care environment, which may not be as applicable to the ED population.

CONCLUSION

Tamsulosin and nifedipine were not more effective than placebo at decreasing the need for urologic intervention at four weeks among patients presenting with acute ureteric colic. The data regarding pain control are less robust and further trials are needed to assess this additional important patient-centered outcome.

Competing Interests: None.

REFERENCES

1. Samad EJ, Hassan S, Farzad R, et al. Therapeutic approaches for renal colic in the emergency department: a review article. *Anesth Pain Med* 2014;4(1):e16222.
2. Preminger GM, Tiselius HG, Assimos DG, et al. 2007 guideline for the management of ureteral calculi. *J Urol* 2007;178(6):2418-34.
3. Türk C, Knoll T, Petrik A, et al. European Association of Urology 2015 Guidelines on Urolithiasis. Available at: http://uroweb.org/guideline/urolithiasis/ (accessed June, 17, 2015).
4. Campschroer T, Zhu Y, Duijvesz D, et al. Alpha-blockers as medical expulsive therapy for ureteral stones. *Cochrane Database Syst Rev* 2014;4:CD008509.
5. Tzortis V, Maoulakis C, Roja J, et al. 2009 Medical expulsive therapy for distal ureteral stones. *Drugs* 2009;69(6):677-92.
6. Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet* 2015;386 (9991):25-31.