REVIEW ARTICLE

Medical Expulsive Therapy for Urinary Stone Disease in Children

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The rising incidence of urinary stone disease in children requires pediatric practitioners to keep abreast of management recommendations which are generally geared towards adults. Medical expulsive therapy (MET) is a non-surgical therapeutic option that can be trialed in patients who present with uncomplicated symptomatic ureteral stones. Seminal articles published and indexed in Medline on the topic of MET were extracted and reviewed. Studies suggest a potential benefit of alpha-blockade for the expulsion of distal ureteral stones that are >5 mm but ≤10 mm in adults and possibly >4 mm in children. Conversely, there does not seem to be any added benefit for MET in smaller stones (<5 mm) in which the spontaneous passage rate is high. **Conclusions**: The off-label use of these medications is one of the several barriers which contribute to the underutilization of MET in children. However, these may be a reasonable option in particular for older children and adolescents with the appropriate-sized stones.

Keywords: *Alpha-blockers, Calculi, Nephrolithiasis, Tamsulosin*.

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Urinary stone disease is a worldwide health problem with increasing incidence and prevalence in developed countries across Europe and Asia [1,2]. Clinical research in urinary stone disease has primarily focused on interventions aimed at reducing the morbidity and costs associated with initial presentation and symptomatic crises as well as long-term preventative strategies. Acute management strategies during a symptomatic event are often dictated by the degree of discomfort, associated infection, or the presence of an acute obstruction with resultant acute kidney injury. Additionally, the location and size of the stone and any associated anatomical abnormality of the urinary tract might impact clinical decision-making [3]. Interventions may involve the administering medications aimed at facilitating stone passage or surgical procedures which directly assist in stone removal. The strategy of administering medications to facilitate the passage of ureteric stones and ameliorate renal colic is generally referred to as medical expulsive therapy (MET). The purpose of this review is to both summarize and critically appraise the MET literature with particular emphasis on children.

BACKGROUND

The ureter contains a layer of smooth muscle which undergoes peristalsis and results in the propulsion of ureteral contents towards the bladder [4]. This can occur both autonomously *via* the release of neurotransmitters and can also be mediated *via* the autonomic nervous system [4].There are multiple different receptors types and second messengers located throughout the ureter which seem to play important roles in mediating this coordinated activity, the most relevant of which are a_1-adrenergic receptors, prostaglandin receptors and phosphodiesterases [4]. Activation of any of the above named receptor sites or increased phosphodiesterase activity typically leads to increased peristalsis [4]. The theoretical principle behind MET is to administer a medication which counteracts the contractile action of the ureters, resulting in smooth muscle relaxation and promoting the passage of stones from the ureter. Medications that have been studied in relation to ureteral stones include a-blockers (*e.g.*, tamsulosin), calcium channel blockers (nifedipine) and phosphodiesterase inhibitors (tadalafil) [5]; although, the latter two medications have not been studied in children [6,7].

In order to adequately assess the effectiveness of MET, one must first consider the natural history and likelihood of spontaneous passage of a stone without medical intervention. In general, stones that are smaller in size have been found to be more likely to pass spontaneously. One study in adults demonstrated that the rate of spontaneous expulsion was 87% for ureteral stones 1 mm in diameter, 76% for stones 2-4 mm, 60% for stones 5-7 mm, 48% for stones 7-9 mm and 25% for those larger than 9 mm [8]. In the pediatric population,

a retrospective study of 33 children revealed that 55% of children with calculi ≤3 mm passed their stones with hydration and narcotic therapy alone. All children with stones >4 mm required further intervention [9]. In addition, adult studies have demonstrated that the location of a stone within the ureter appears to affect the likelihood of spontaneously passage. Distal and ureterovesicular junction had the highest rate of spontaneous expulsion at 75% and 79%, respectively, followed by mid ureteral and proximal ureter stones with rates of 60% and 48% [8]. Other less well defined factors that may play a role include number of stones, and the degree of edema in the ureters [10].

A meta-analysis of nine randomized controlled trials (1981-2005) reported on 693 adults using a-blockers or calcium channel blockers as the primary therapy for MET and stone passage as the primary outcome [11]. The authors determined that subjects who received either tamsulosin or nifedipine had a 1.65 higher chance (95% CI, 1·45-1·88) of passing their stones. Based on this study and similar meta-analyses [12], both the European Association of Urology (EAU) and American Urologic Association (AUA) included recommendations that allowed for patients with stones <6 mm or stones <10 mm, respectively, the option of a trial of MET [6,7].

Adult studies: The Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial consisted of 1167 adults with a ureteral stone <10 mm. Subjects were randomized to receive either nifedipine 30 mg, tamsulosin 0.4 mg or placebo [13]. There was no difference between active treatment with MET and placebo or between tamsulosin and nifedipine. Further, no benefit was seen in patients with respect to stone size or location in the ureter [13]. Similar to the SUSPEND trial, Furyk, *et al*. [14] also reported no difference in overall rates of stone passage between patients in tamsulosin or placebo groups. Importantly, in the subgroup with stones >5 mm there was a 22.4% (95% CI 3.1 to 41.6, *P*=0.03) higher rate of stone passage in those who received tamsulosin as compared to the placebo group [14]. The Tamsulosin for Urolithiasis in the Emergency Department (STONE) study [15] did not find a significantly better stone passage rate in patients who received MET, as compared to placebo. In the largest randomized, double blind placebo controlled study to date, Ye, *et al*. [16] examined the difference in distal ureteral stone expulsion rates in 3296 patients receive either 0.4 mg tamsulosin or placebo for 28 days [16]. Results from the study demonstrated a statistically significant benefit for those patients who received tamsulosin (86% stone passage) versus those receiving placebo (79% stone passage) with a *P*-value <0.001 [16]. Patients treated with tamsulosin were also found to pass the stones sooner than those on placebo (148.3 *vs* 248.7 hours) [16]. Subgroup analysis demonstrated that there was no benefit for tamsulosin therapy for subjects with stones ≤5 mm and that the entire beneficial effect was driven by those subjects with stones >5 mm. These results perhaps explain the discrepant findings noted between the previous randomized controlled studies in which the majority of stones were small and underpowered to evaluate size effect.

In 2016, an updated meta-analysis of 55 randomized controlled trials (including 5990 patients) that evaluated the effect of alpha blockers on ureteral stone expulsion was performed by Hollingsworth, *et al*. [17]. The pooled risk ratio (RR) for stone expulsion was 1.49 (95% CI 1.39 to 1.61) for patients treated with alpha blockers as compared to those who were treated with placebo [17]. The effect of MET in relation to the location of the stone revealed that Tamsulosin increased the rate of stone passage in the upper and middle ureter (pooled RR of 1.48 with 95% CI 1.05 to 2.10) and confirmed the benefit in distal ureteral stones (pooled RR of 1.49 with 95% CI 1.38 to 1.63) as compared to controls [17].

In summary it appears that MET, and in particular alpha blockade, has beneficial effects on aiding expulsion of ureteral stones >5 mm in size in adults. This benefit appears to be most consistent for stones found in the distal ureter but may be beneficial for the management of stones >5 mm and <10 mm regardless of location.

Pediatric studies: There are multiple factors which contribute to the limited use of MET in pediatric patients. These include a lack of familiarity with MET by pediatric practitioners, a relatively larger stone size to the ureteral dimension ratio as compared to adults, physician and parental discomfort with off-label use of medications in children, and a fear of potential poor tolerance of alpha-blockers [18]. To highlight this point Ellison, *et al*. [19] performed a retrospective study using the Market Scan Commercial Claims and Encounters database to assess how often MET was being offered to pediatric patients [19]. Overall 1325 children between the ages of 1-18 years with either a renal or ureteral calculus were identified by ICD 9 code. Of these only 13.2% received MET [19]. Nonetheless, several studies have examined the efficacy of MET in the management of distal ureteral stones in the pediatric population with mixed results.

A prospective, randomized trial of 39 children with ureteral stones <10 mm in size compared the efficacy of ibuprofen alone as compared to doxazosin (0.03 mg/kg daily) on stone passage rates [20]. During a mean follow up period of 19 days, there was no significant difference between the groups in terms of expulsion rates and mean

time to expulsion [20]. Conversely, Erturhan, *et al*. demonstrated a benefit of doxazosin as compared to analgesia alone in a study of 45 children with distal ureteral calculi at three weeks follow-up [21]. In this study, only 28.6% patients in the control group had spontaneous expulsion of their stones as compared to 70.8% in the intervention group (P=0.005) [21]. It is noteworthy; however, that the spontaneous expulsion rate in the control group was substantially lower than what has been reported in other similar pediatric studies [10,20,22], thus potentially magnifying the effect of the MET.

Several studies have also examined the effect of tamsulosin in children. A placebo-controlled prospective trial in which 61 children with distal ureteral stones <12 mm were randomized to receive either analgesia plus tamsulosin or analgesia with placebo, found that after four weeks, patients who received tamsulosin were significantly more likely to have spontaneous stone passage (87.8%) as compared to the placebo group (64.2%) [10]. Additionally there was a significant difference in time to passage of the stone with those in the tamsulosin group passing stones on average 6 days earlier than the control group [10]. Aldaqadossi, *et al*. [22] demonstrated similar findings in 67 pediatric patients with distal ureteral stones <10 mm; 87% of 33 children receiving tamsulosin passed their stones with a mean time of 7.7 days while only 63% of the 34 controls passed their stones with a mean time of 18 days [22]. A multi-center retrospective study compared 99 children prescribed tamsulosin for ureteral stones <10 mm to 99 propensity matched controls who were treated with analgesia alone [23]. At six week follow up, 55% of patients receiving MET achieved stone expulsion as compared to 44% of controls (P=0.03) [23]. Logistic regression analysis adjusting for stone size and location showed an odds ratio of 3.31 (95% CI 1.49-7.34) for spontaneous stone passage in children receiving tamsulosin as compared to those receiving analgesia alone [23].

To date two pediatric meta-analyses have been performed. A meta-analysis [24] including four of the previously cited studies [10,20,21,23] and one abstract [25] included 465 subjects <18 years of age with ureteral stones demonstrated that MET significantly increased the odds of spontaneous stone passage (OR 2.21, 95% CI 1.40 -3.49) as compared to controls. Furthermore, when the analysis was restricted to the randomized controlled trials [10,20,21], MET significantly increased the odds of spontaneous stone passage (OR 4.06, 95% CI 1.84-8.95) as compared to controls [24]. The second meta-analysis [26] included 406 children who were treated exclusively with a-blockers from four of the previously cited prospective trials [10,20-22] and one cohort study [23]. This analysis also demonstrated a higher stone expulsion rate (OR 2.71, 95% CI 1.49-4.91) associated with MET usage but did not demonstrate shorter times to stone passage as compared to controls [26].

CONCLUSION

Pediatric urinary stone disease is an evolving condition whose incidence and prevalence have increased over the last several decades [27]. In response to this increased burden, MET has been well studied and guidelines for its use in adults are already available [7,28]. The most frequently studied medication has been tamsulosin, which potentially contributes to stone passage through the relaxation of ureteral smooth muscle thereby promoting the promoting the passage of stones. Notably, stones <4-5 mm have a high likelihood of spontaneous passage resulting in seemingly little added benefit of MET. Conversely, adult studies seem to suggest that MET likely may increases the likelihood of stone passage in patients with distal ureteral stones >5 mm and <10 mm in size. Although, studies in children are few in number and contain a limit number of patients, most studies indicate that tamsulosin might be of benefit in children with ureteral stones ≥ 4 mm but less than 10-12mm [9].

REFERENCES

1. Romero V, Akpinar H, Assimos DG. Kidney Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors. Rev Urol. 2010;12:e86-e96.
2. Scales CD Jr, Smith AC, Hanley JM, Saigal CS. Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62:160-65.
3. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, *et al*. 2007 Guideline for the Management of Ureteral Calculi. Eur Urol. 2007;52:1610-31.
4. Canda AE, Turna B, Cinar GM, Nazlý O. Physiology and Pharmacology of the Human Ureter: Basis for Current and Future Treatments. Urol Int. 2007;78:289-98.
5. Kroczak T, Pace KT, Lee JY. Medical Expulsive Therapy: Worthwhile or wishful thinking. Curr Urol Rep. 2017;18:29.
6. Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, *et al.* Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. J Urol. 1997;158:1915-21.
7. Türk C, Knoll T, Seitz C, Skolarikos A, Chapple C, McClinton S. Medical expulsive therapy for ureterolithiasis: The EAU Recommendations in 2016. Eur Urol. 2017;71:504-7.
8. Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. Am J Roentgenol. 2002;178:101-3.
9. Van Savage JG, Palanca LG, Andersen RD, Rao GS,

Slaughenhoupt BL. Treatment of distal ureteral stones in children: Similarities to the American Urological Association guidelines in adults. J Urol. 2000;164:1089-93.
10. Mokhless I, Zahran AR, Youssif M, Fahmy A. Tamsulosin for the management of distal ureteral stones in children: A prospective randomized study. J Pediatr Urol. 2012;8:544-8
11. Hollingsworth JM, Rogers MA, Kaufman SR, Bradford TJ, Saint S, Wei JT, *et al.* Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet. 2006;368:1171-9.
12. Seitz C, Liatsikos E, Porpiglia F, Tiselius HG, Zwergel U. Medical therapy to facilitate the passage of stones: what is the evidence? Eur Urol. 2009;56:455-71.
13. Pickard R, Starr K, maclennan G, Lam T, Thomas R, Burr J, *et al*. Medical expulsive therapy in adults with ureteric colic: A multicentre, randomised, placebo-controlled trial. Lancet. 2015;386:341-9.
14. Furyk JS, Chu K, Banks C, Greenslade J, Keijzers G, Thom O, *et al.* Distal ureteric stones and tamsulosin: A double-blind, placebo-controlled, randomized, multicenter trial. Ann Emerg Med. 2016;67:86-95.e2.
15. Meltzer AC, Burrows PK, Wolfson AB, Hollander JE, Kurz M, Kirkali Z, *et al.* Effect of tamsulosin on passage of symptomatic ureteral stones: A randomized clinical trial. JAMA Intern Med. 2018;178:1051-7.
16. Ye Z, Zeng G, Yang H, Tang K, Zhang X, Li H, et al. Efficacy and safety of tamsulosin in medical expulsive therapy for distal ureteral stones with renal colic: A multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol. 2018;73:385-91.
17. Hollingsworth JM, Canales BK, Rogers MAM, Sukumar S, Yan P, Kuntz GM, *et al.* Alpha blockers for treatment of ureteric stones: Systematic review and meta-analysis. BMJ. 2016;355(6112).
18. Cerwinka WH. Commentary to "Utilization of medical expulsive therapy in children: An Assessment of nationwide practice patterns and outcomes. J Pediatr Urol. 2017;13:510.
19. Ellison JS, Merguerian PA, Fu BC, Holt SK, Lendvay TS, Gore JL, *et al.* Use of medical expulsive therapy in children: An assessment of nationwide practice patterns and outcomes. J Pediatr Urol. 2017;13:509.e1-509.e7.
20. Aydogdu O, Burgu B, Gucuk A, Suer E, Soygur T. Effectiveness of Doxazosin in treatment of distal ureteral stones in children. J Urol. 2009;182:2880-4.
21. Erturhan S, Bayrak O, Sarica K, Seckiner I, Baturu M, Sen H. Efficacy of medical expulsive treatment with Doxazosin in pediatric patients. Urology. 2013;81:640-3.
22. Aldaqadossi HA, Shaker H, Saifelnasr M, Gaber M. Efficacy and safety of tamsulosin as a medical expulsive therapy for stones in children. Arab J Urol. 2015;13:107-11.
23. Tasian GE, Cost NG, Granberg CF, Pulido JE, Rivera M, Schwen Z, *et al.* Tamsulosin and spontaneous passage of ureteral stones in children: A multi-institutional cohort study. J Urol. 2014;192:506-11.
24. Velazquez N, Zapata D, Hsin-Hsiao SW, Wiener JS, Lipkin ME, Routh JC. Medical expulsive therapy for pediatric urolithiasis: Systematic review and meta-analysis. J Pediatr Urol. 2015;11:321-7.
25. George A, Montag S, Cubillos J, Gitlin J, Palmer LS. The effect of tamsulosin on ureterolithiasis in the pediatric population. J Urol. 2011;185:e552-e53.
26. Tian D, Li N, Huang W, Huantao Z, Zhang Y. The efficacy and safety of adrenrgic alpha-antagonists in treatment of distal ureteral stones in pediatric patients: A systematic review and meta-analysis. J Pediatr Surg. 2017;52:360-65.
27. Scales CD, Tasian GE, Schwaderer AL, Goldfarb DS, Star RA, Kirkali Z. Urinary stone disease: Advancing knowledge, patient care, and population health. Clin J Am Soc Nephrol. 2016 ;11:1305-12.
28. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, *et al*. Medical management of kidney stones: AUA Guideline. J Urol. 2014;192:316-24.