



PEDIATRIC UROLOGY
ORIGINAL ARTICLE

Efficacy and safety of tamsulosin as a medical expulsive therapy for stones in children



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Received 12 December 2014, Received in revised form 22 January 2015, Accepted 13 February 2015
Available online 9 March 2015

KEYWORDS

Distal ureteric calculi;
Medical expulsive
therapy;
Children;
Tamsulosin

ABBREVIATIONS

MET, medical expul-
sive therapy;
US, ultrasonography;
BP, blood pressure

Abstract Objectives: To evaluate the efficacy of tamsulosin for promoting ureteric stone expulsion in children, based on the confirmed efficacy of tamsulosin as a medical expulsive therapy in adults.

Patients and methods: From February 2010 to July 2013, 67 children presenting with a distal ureteric stone of < 1 cm as assessed on unenhanced computed tomography were included in the study. The patients were randomised into two groups, with group 1 (33 patients) receiving tamsulosin 0.4 mg and ibuprofen, and group 2 (34) receiving ibuprofen only. They were followed up for 4 weeks. Endoscopic intervention was indicated for patients with uncontrolled pain, recurrent urinary tract infection, hypersensitivity to tamsulosin and failure of stone passage after 4 weeks of conservative treatment.

Results: Sixty-three patients completed the study. There were no statistically significant differences between the groups in patient age, body weight and stone size, the mean (SD) of which was 6.52 (1.8) mm in group 1 vs. 6.47 (1.79) mm in group 2 ($P = 0.9$). The mean (SD) time to stone expulsion in group 1 was 7.7 (1.9) days, vs. 18 (1.73) days in group 2 ($P < 0.001$). The analgesic requirement (mean number of

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Peer review under responsibility of Arab Association of Urology.



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ketorolac injections) in group 1 was significantly less than in group 2, at 0.55 (0.8) vs. 1.8 (1.6) ($P < 0.001$). The stone-free rate was 87% in group 1 and 63% in group 2 ($P = 0.025$).

Conclusions: Tamsulosin used as a medical expulsive therapy for children with ureteric stones is safe and effective, as it facilitates spontaneous expulsion of the stone.

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Introduction

Contemporary studies report an increase in the incidence of urolithiasis in children, mostly due to changes in dietary habits, climate changes, and the widespread use of ultrasonography (US) for examination of nonspecific conditions. Generally the incidence of paediatric urolithiasis is 2–3%. Published data on the predominance with gender are variable. Ureteric stones comprise about 20% of diagnosed urinary calculi [1]. Older children usually present with classic symptoms of calculi, such as loin pain, dysuria or haematuria. However, nonspecific symptoms, like irritability, are common in younger children who cannot express themselves [2].

The factors affecting the urologist's decision when recommending treatment for patients with ureteric calculi include the stone location and size, the degree of back-pressure, and associated UTI. Currently, with the development of smaller and more durable endoscopic equipment, the management of ureteric stones in children has developed from open stone surgery to minimally invasive procedures [3]. One approach to the treatment of ureteric calculi is observation, with pharmacotherapy used to relieve any pain. This might be a good choice, as it avoids the risk of anaesthesia and the cost of interventional techniques [4]. Several studies reported that medical expulsive therapy (MET) is effective in promoting the passage of distal ureteric stones in adults.

For this therapy, α -adrenergic blockers are the preferred agent for MET [5]. Tamsulosin was first indicated in children by Donohoe et al. [6] as a therapy for primary bladder neck dysfunction, with no major side-effects. The USA Food and Drug Administration Paediatric Advisory Committee in January 2012 reviewed studies on the use of tamsulosin in children and recommended returning to routine safety monitoring.

The aim of the present study was to evaluate the efficacy of tamsulosin in promoting the spontaneous expulsion of distal ureteric stones in children, based on the confirmed efficacy of tamsulosin as MET in adults.

Patients and methods

From February 2010 to July 2013, 67 children presenting with a distal ureteric stone of <1 cm, and below

the common iliac vessels as assessed by unenhanced CT, were included in the study. All patients were fully evaluated by a detailed history, physical examination, laboratory examinations (urine analysis, blood urea and serum creatinine levels), and radiological tests (a plain abdominal film, urinary tract US, and unenhanced CT of the abdomen and pelvis). The patients were randomised into two groups; group 1 included 33 patients who received tamsulosin 0.4 mg and ibuprofen, and group 2 included 34 patients who received ibuprofen only. The method of randomisation was simple random allocation of the children into the study groups. Patients who could not swallow a tamsulosin capsule were allowed to evacuate the contents into water or juice. Patients were excluded if they had bilateral ureteric stones, multiple stones, marked hydronephrosis, UTI, urinary tract anomalies, voiding dysfunction, and any previous open or endoscopic ureteric surgery.

Tamsulosin was administered using an arbitrary dose of 0.4 mg for patients aged >5 years and 0.2 mg for younger children. The drug was given at bedtime. We discussed with families the off-label use of tamsulosin and the possible side-effects, e.g., headache, dizziness, rhinitis, back pain, somnolence and sinusitis. The ibuprofen dose was 4–10 mg/kg orally every 6–8 h as needed. In the case of intractable pain, ketorolac 0.5–1 mg/kg was given intramuscularly. The blood pressure (BP) with the child seated was measured before the administration of therapy and at each subsequent visit, to record any change in haemodynamics.

The study was approved by the local ethics committee, and informed consent was obtained from the parents. The guardians of enrolled children were instructed to give their children the study medication, and to filter the child's urine to identify passed stones. Also, they used a diary to record the amount of required analgesics, the number pain attacks, the time of stone expulsion, and any side-effects of study medication.

The patients were assessed clinically every week with a measurement of BP, urine analysis, a plain film if the stone was radio-opaque, and with US if the stone was radiolucent. A radiolucent lower ureteric stone can be assessed by US directly by looking at an acoustic shadow with a negative background, and indirectly by looking at hydronephrosis proximal to the stone. The

duration of the follow-up was 4 weeks. Endoscopic intervention was indicated for patients with uncontrolled pain, recurrent UTI, hypersensitivity to tamsulosin and failure of stone passage by the end of 4 weeks of conservative treatment.

The primary endpoint was the spontaneous stone expulsion rate, confirmed by a plain film and US. Secondary endpoints were the interval to stone passage, the amount of analgesic required, the reported painful episodes, and the side-effects and safety of tamsulosin.

The results were analysed statistically using an independent Student's *t*-test for parametric data and the Mann–Whitney *U*-test for nonparametric data, after using the Kolmogorov–Smirnov test of normality. In all analyses $P < 0.05$ was considered to indicate statistical significance.

Results

Of the 67 children, four were lost during the follow-up and so 63 patients were included in the evaluation. There were no statistically significant differences in age, body weight and stone size between the groups (Table 1). The stone-free rate was significantly higher in group 1 than in group 2, at 87% vs. 63%, respectively ($P = 0.025$). In group 1 there was a statistically significant advantage in the mean time to stone expulsion ($P < 0.001$; Table 1). The mean number of daily pain episodes in group 1 was significantly less than in group 2 ($P = 0.03$; Table 1), and the analgesic requirement (mean number of ketorolac injections during the study) in group 1 was significantly less than in group 2 ($P < 0.001$). Three of the 31 patients receiving tamsulosin in group 1 reported mild degrees of nasal

congestion, but no major side-effects were reported. The values of BP were within normal levels in all children during the study period, with no significant differences between the groups ($P = 0.8$; Table 1). In group 1 the mean BP (systolic/diastolic) at baseline was 94.2 (8.4)/60.2 (5.1) mmHg and during the follow-up it was 93.6 (10.0)/61.1 (6.2) mmHg.

Discussion

Calculi can occur at any age in children, with calcium stones being the most common type (57%), followed by struvite (24%), uric acid (8%), cystine (6%), endemic (2%), mixed (2%) and other types (1%). The factors responsible for the development of stones in children include metabolic disturbances, UTIs, anatomical anomalies, diet and environment [7]. The recent miniaturisation of ureteroscopes and growing endourological expertise have resulted in greater success in the management of ureteric stones in children by ureteroscopy. However, ureteroscopy is associated with the risk of anaesthesia and the probability of ureteric trauma and stricture.

There is also a chance for the spontaneous passage of small stones. All these factors should be considered before intervention [4]. There are several factors affecting the chance of spontaneous passage of distal ureteric calculi, such as the size, site and number of stones, and ureteric spasm and oedema. Stone size has been reported to be the main predictive factor for the spontaneous passage of ureteric stones, with a linear relationship [8]. In adults, according to published data, the chance of spontaneous stone passage for distal ureteric stones of ≤ 5 mm is 71–98%, but only 25–51% for those of

Table 1 The characteristics and results of the children in the two groups.

Mean (SD), <i>n</i> or <i>n</i> (%) variable	Group (<i>n</i>)		<i>P</i>
	1 (31)	2 (32)	
Age (years)	7.7 (3.02)	7.25 (2.70)	0.5
Male	17 (55)	19 (59)	
Female	14 (45)	13 (41)	
Weight (kg)	22.1 (5.8)	23.0 (5.6)	0.5
Stone size (mm)	6.52 (1.8)	6.47 (1.79)	0.9
< 5	9	7	
> 5	22	25	
Right	14	18	
Left	17	14	
BP (mmHg)			
Systolic	93.6 (10.0)	94.1 (10.0)	0.8
Diastolic	61.1 (6.2)	62.7 (5.8)	0.8
Time to stone	7.7 (1.9)	18 (1.73)	< 0.001
Expulsion (days)			
Daily pain	1.6 (1.6)	2.5 (1.9)	0.03
Episodes (<i>n</i>)			
Analgesic requirement*	0.55 (0.8)	1.8 (1.6)	< 0.001
Stone-free rate (%)	87	63	0.025

* Mean number of ketorolac injections during the study.

> 5 mm, but the data on spontaneous stone passage in children are limited [4]. Van Savage et al. [9] reported that stones of < 3 mm in diameter in the distal ureter of children have a greater chance of passing spontaneously, but stones of ≥ 4 mm in the distal ureter usually require intervention. However, Pietrow et al. [10] concluded that the passage rate of ureteric stones is consistent in adults and children, with stones of > 5 mm unlikely to pass spontaneously.

The goals of conservative treatment are to relieve pain and to prevent factors interfering with spontaneous stone expulsion, such as oedema, spasm and infection [11]. α -Blockers have been used as MET for ureteric stones, suggested by many physiological studies. The ureteric smooth muscles are supplied with α -adrenergic receptors, especially in the distal third of the ureter. α -Adrenergic blockers inhibit basal smooth muscle tone and hyper-peristaltic uncoordinated frequency, with no effect on tonic propulsive contractions [12]. Since 2002, several studies have reported the beneficial effect of α -blockers in increasing the likelihood of the spontaneous passage of ureteric stones, as α -blockers lower the ureteric muscle tone and intramural pressure [5,13].

Although MET has been studied extensively in adults, studies on the role of α -blockers in the management of distal ureteric calculi in children are limited. The non-selective α -blocker phenoxybenzamine was used by McGuire and Weiss [14] for treating bladder neck obstruction in boys secondary to a posterior urethral valve. Austin et al. [15] concluded that doxazosin was effective and safe in children with a weak urinary flow rate. Donohoe et al. [6] used α -blockers in children with primary bladder neck obstruction, reporting that α -blockers were effective and well tolerated, especially tamsulosin, with no major adverse effects (palpitation, or postural hypotension). Also, they reported mild to moderate degrees of headache, somnolence, nasal congestion or dizziness in 75% of children treated with α -blockers.

Some have used α -blockers as MET for distal ureteric calculi in children, based on their efficacy and safety in paediatric voiding dysfunction and in adults with distal ureteric stones. In a prospective randomised study, Aydogdu et al. [16] found that the spontaneous stone expulsion rate was 70% in children treated with analgesics and 84% in those who received tamsulosin ($P > 0.05$), with no significant difference between the groups in spontaneous expulsion rate and mean expulsion time. Mokhless et al. [17] evaluated 61 children with distal ureteric stones, and reported a statistically significantly higher stone-free rate in children treated with tamsulosin and analgesia (group I) than in children treated with analgesia and placebo (group II) (87.8% and 64.2%, respectively; $P < 0.001$). The mean stone expulsion time was shorter in group I than in group II, and this difference was statistically significant

($P < 0.001$). In all, 45 children with a distal ureteric stone were enrolled in a study by Erturhan et al. [18], and randomised into two groups, the first treated with ibuprofen and the second with ibuprofen and doxazosin. The stone-free rate was significantly higher in the second group, with statistically significantly fewer colic attacks and quicker stone passage. In a multi-institutional retrospective study, Tasian et al. [19] concluded that the rate of spontaneous expulsion of ureteric stones was higher in children who received tamsulosin than in those managed by analgesics only. They also noted that there were no side-effects related to tamsulosin use.

There are few studies evaluating α -blockers as MET for distal ureteric stones in children, so we devised the present study to contribute to the existing data. We used tamsulosin in doses that were reported to be effective in adults, and safe in children. Lojanapiwat et al. [20] reported that tamsulosin at a low dose (0.2 mg daily) and standard dose (0.4 mg daily) for distal ureter calculi was effective as MET, with no significant difference between the doses. In the present study the dose of tamsulosin in children aged < 5 years was 0.2 mg daily, whilst in older children it was 0.4 mg daily. Tamsulosin significantly increased the spontaneous stone expulsion rate within a short time (87% vs. 63%, $P = 0.025$), and significantly decreased the number of colic episodes and the need for analgesics. This is consistent with previous results [17–19]. However, Aydogdu et al. [16] found that there was no statistically significant advantage of an α -blocker used as MET in children.

Only three children in group I had mild degrees of nasal congestion, and no major adverse effects, e.g., postural hypotension, were reported. In group I the mean BP at baseline and during the study were not significantly different, and during the follow-up there were no significant differences between the groups in mean BP ($P = 0.8$; Table 1). Based on the present study, tamsulosin seems to be a safe therapy that facilitates the spontaneous passage of stones in children.

In conclusion, tamsulosin as MET for a ureteric stone in children is safe and effective, as it facilitates spontaneous expulsion of the stone.

Conflict of interest

None.

Source of funding

None.

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