African Journal of Urology (2017) **23**, 38–42

African Journal of Urology

Official journal of the Pan African Urological Surgeon's Association
web page of the journal

www.ees.elsevier.com/afju
www.sciencedirect.com

Original article

Preliminary study of the efficacy of the combination of tamsulosin and trospium as a medical expulsive therapy for distal ureteric stones

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Received 12 August 2015; received in revised form 16 February 2016; accepted 20 February 2016
Available online 13 December 2016

KEYWORDS
Trospium;
Tamsulosin;
Ureter;
Ureteral calculi;
Medical expulsive therapy

Abstract
Objectives: To evaluate and compare the efficacy of tamsulosin (0.4 mg, once/day) and combinations of it with trospium (20 mg, twice/day) in the treatment of single small lower ureteral stones.
Patients and methods: A total of 126 patients presenting to urology outpatient clinics from July 2012 to May 2015, with a single 5–10 mm sized lower ureteral stone were randomly classified into two treatment groups. Patients in group A (n = 62) received an oral dose of 0.4 mg tamsulosin once daily and 20 mg trospium chloride twice daily. Patients in group B (n = 64) received 0.4 mg tamsulosin once daily and placebo twice daily. The spontaneous passage of stones, the stone expulsion time, and adverse effects were evaluated.
Results: There were no significant differences in baseline characteristic of the patients in both groups. Stone expulsion was observed in 47 patients (75.8%), and 58 (90.62%) in groups A and B respectively. The average time to expulsion was 11.65 ± 5.32 days in group A and 17.35 ± 6.21 days in group B. The spontaneous stone passage rate through the ureter was significantly higher and the stone expulsion time was faster in groups A than in group B ($p < 0.05$). The adverse effects observed in both groups were comparable and were mild.

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Peer review under responsibility of Pan African Urological Surgeons' Association.

http://dx.doi.org/10.1016/j.afju.2016.02.006

Conclusions: The combination of 0.4 mg tamsulosin and 40 mg trospium as MET for single lower ureteral stones <10 mm is safe and more effective than 0.4 mg tamsulosin as a mono-therapy.

Introduction

Urinary tract stones account for 20% of urology in patients and affect approximately 5% of people worldwide. The lifetime risk of urinary tract stones is approximately 20% in Saudi Arabia while the risk is 10%–15% in the USA and 5%–19% in Europe [1]. Stone location (upper, mid, and lower), size, chemical composition and associated complications are the most important determining factors in the treatment of urinary tract stones.

Treatments of lower ureteral stones are divided into three categories: (1) observation and medical therapy, (2) shock wave lithotripsy (SWL) ureteroscopy, and (3) open surgery laparoscopic stone removal. AUA/EUA guidelines recommend watchful waiting with medical treatment for patients with a lower ureteral stone <10 mm in diameter and well-controlled pain [2].

There is growing evidence that medical expulsive therapy (MET) augments the expulsion rate of ureteral stones. Alpha-blockers are still the most promising stone-expulsive agents. They act mostly through selective relaxation of ureteral smooth muscle, which results in the release of ureteral spasms and dilatation of the ureteral lumen, especially the distal part of the ureter [3–5].

Many different types of antispasmodic agents may have an analgesic effect by inducing smooth muscle relaxation and releasing ureteral spasms. This likely explains why these antispasmodic agents are recommended for the treatment of renal colic. Several studies have assessed anti-spasmodic agents, focusing on their role in colic pain management [6–8]. However, in our prospective randomised study, we aimed to compare the impact of 0.4 mg tamsulosin and 40 mg trospium as a combination treatment on stone expulsion rate and colicky pain versus 0.4 mg tamsulosin alone in patients with lower ureteral stones from 5 to 10 mm in diameter.

Patients and methods

Our prospective double blind randomised study included 126 patients with single lower ureteral stones from 5 to 10 mm selected from an emergency department and urology outpatient clinic over the period from July 2012 to May 2015. All patients were evaluated via detailed clinical history, physical examination, urine analysis and serum creatinine, plain X-ray urinary tract, urinary tract ultrasound and intravenous urography for evaluation of stone site, size and pelvicalyceal system dilatation and state of ureter (normal or stricture ureter).

The exclusion criteria were pregnancy, age below 18 years old, presence of urinary tract infection, renal insufficiency, solitary kidney, multiple stones, a previous history of distal ureter surgery, bilateral ureteral stones, moderate or severe hydronephrosis, current alpha-blocker use and allergic reaction to tamsulosin and trospium chloride. When the patient met our inclusion criteria; the assigned treatment was disclosed and fully explained before obtaining informed patient consent. A signed informed consent form was obtained from the participants, who were then randomised into treatment groups. A total of 126 patients were thus classified into two treatment groups. Patient group A (n = 62) received 0.4 mg tamsulosin once daily and a placebo twice daily. Patients in group B (n = 64) received an oral dose of 0.4 mg tamsulosin once daily and 20 mg trospium chloride twice daily. All patients received 50 mg diclofenac sodium on demand. Drug administration was started immediately after diagnosis and continued for a maximum of 30 days or until spontaneous stone expulsion or an alternative treatment was applied.

Follow-up visits were performed on days 7, 14, 21 and 30. At each follow-up visit, we evaluated spontaneous passage of stones, stone expulsion time and side effects. At each visit, all patients underwent basic specific evaluations including a plain KUB, ultrasonography, urine analysis and serum creatinine. In addition, all patients were asked to drink at least 2 L of fluid daily, and we recorded the type and number of analgesics taken during the course of treatment as well as any associated complaints or consultations.

Of 189 patients with lower ureteric stone patients, 142 met the inclusion criteria; and accepted to participate in the study. From the remaining 142, 16 patients were excluded due to noncompliance issues, development of urinary tract infection, lost follow-up during the follow-up period in both group. Hence, we left with a total of 126 patients: 62 patients in Tamsulosin group and 64 patients in combinations group (Fig. 1).

Statistical analyses

Statistical analysis of our study was done using SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA) software. A one-way analysis of variance was used to compare continuous variables between the two different groups, and different continuous variables between both groups were tested with a Student's t-test. All parameters were analysed using Pearson's chi-square and Fischer's exact test, and a p-value <0.05 was considered significant.

Results

Patient characteristics

The mean stone size was 6.69 ± 1.34 mm for group A and 6.91 ± 1.64 mm for group B. There were no statistically significant differences between the two groups in regard to patient characteris-

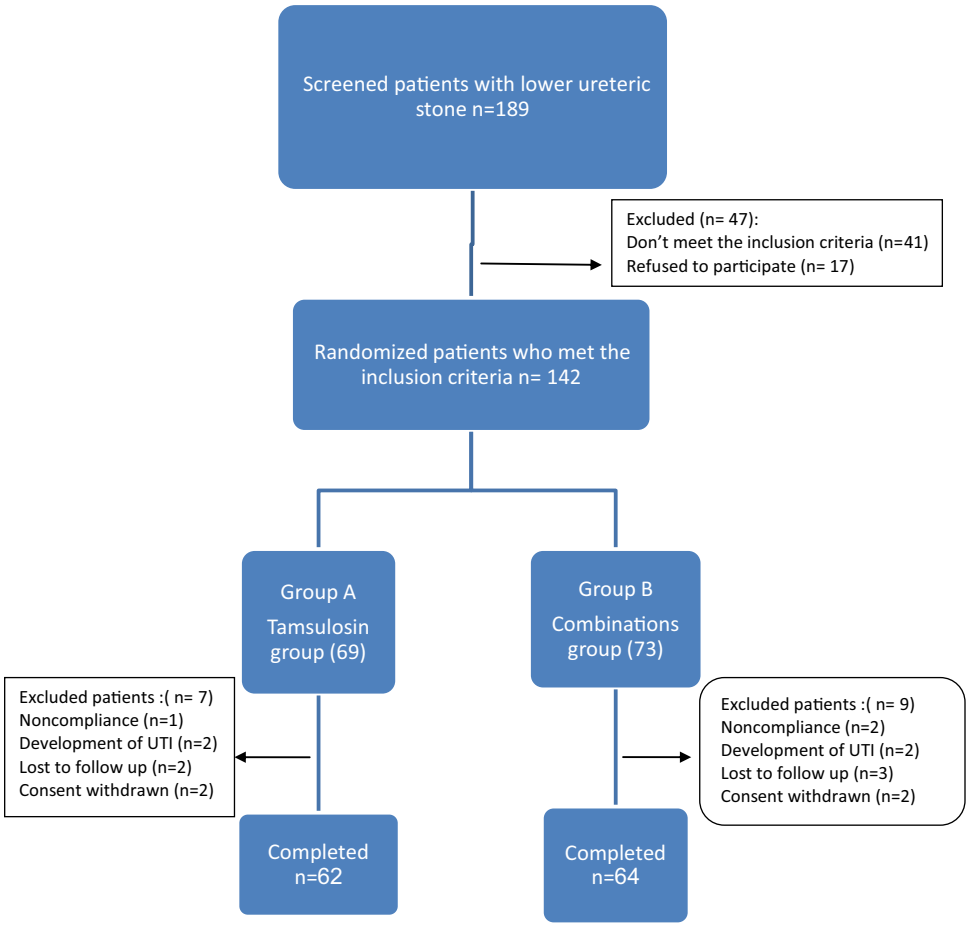

Figure 1 Patients' disposition. UTI "urinary tract infections".

Table 1 Baseline patient characteristics.

Characteristic	Group A (n = 62) Tamsulosin group	Group B (n = 64) Combinations group	p Value
Mean age (year)	39.02 ± 8.7	36.43 ± 6.7	>0.05
Sex (male:female)	31:11	30:14	>0.05
Body mass index (kg/m^2)	26.12 ± 1.02	25. 15 ± 1.34	>0.05
Stone size (mm)	6.69 ± 1.34	6.91 ± 1.64	>0.05
Stone side (right to left)	19:23	20:24	>0.05
Symptoms durations (day)	5.3 ± 2.8	5.9 ± 2.7	>0.05

tics (age, sex, body mass index) or stone characteristics (stone size, stone site or complaint duration). The demographic data of the study patients and stones are summarised in Table 1.

Stone expulsion rate and time

Stone expulsion was observed in 47 patients in group A (75.8%) and 58 patients in group B (90.62%), and the mean time to stone expulsion was 17.35 ± 6.21 days in group A and 11.65 ± 5.32 days in group B (Table 2).

Side effects observed in the study groups

No severe complications were observed in either group. Retrograde ejaculation was recorded in 5 patients (8.06%) in group A and 4 patients (6.25%) in group B, and there were no statistically significant differences in terms of headache, dizziness, diarrhoea, fatigue, nausea or vomiting (p > 0.05) (Table 3).

During the study period, none of the patients complained of persistent agonising pain or the development of complicated fever or severe obstructive uropathy that required urgent intervention. A total of 21 patients did not pass the stone within 4 weeks, and these patients were successfully treated by ureteroscopy (Fig. 1).

Discussion

The AUA/EAU guidelines suggest that MET is an acceptable treatment choice for selected patients with early diagnosis of ureteral stones less than 8 mm and in cases when urgent stone removal is

Table 2 Stone expulsion rate and time.

	Group A (n = 62) Tamsulosin group	Group B (n = 64) Combinations group	p Value
Stone expulsion rate at one months	47 (75.8%)	58 (90.62%)	<0.05
Mean days to stone expulsion	17.35 ± 6.21	11.65 ± 5.32	<0.05
Numbers of colicky pain	3.2 ± 2.1	2.8 ± 1.8	<0.05
Diclofenac consumption	620–810 (660 ± 130)	430–600 (490 ± 95)	<0.05

Table 3 Side effects observed in the study group.

Characteristic	Group A (n = 62) Tamsulosin group		Group B (n = 64) Combinations group		p Value
Retrograde ejaculation	5	8.06%	4	6.25%	>0.05
Orthostatic hypotension	2	3.2%	2	3.1%	>0.05
Headache, dizziness	3	4.83%	2	3.1%	>0.05
Constipation-dry mouth	1	1.6%	5	7.8%	<0.05
Fatigue	3	4.83%	3	4.68%	>0.05

not indicated and observation with periodic evaluation is an initial option. Previous studies have demonstrated that the MET has a significant positive impact on stone expulsion rates. Moreover, the use of MET is not limited to only those patients attempting passage of calculi without other interventions [2,4,5]. MET is also advantageous for patients treated with other modalities (i.e. SWL and ureteroscopy), potentially reducing medical costs and preventing unnecessary surgeries and their associated risks [4,5].

Bos and Kapoor recommend alpha-blockers as the current best practice for conservative management of distal ureteral stones, in comparison to other expulsive medical treatments such as calcium channel blockers, which remain inferior to alpha-blockers; for example, PDE5 inhibitors and corticosteroid remain insufficient for distal ureteral stones and yield non-significant results [9].

Spontaneous stone passage occurs for 68% of stones less than 5 mm and for 47% of stones more than 5 mm in diameter, and distal stones are more likely to pass spontaneously. Miller and Kane reported that stone size and location are the most important predictive factors for spontaneous stone passage [10].

The lower ureter is composed of transitional epithelium, a connective tissue layer and three layers of smooth muscle. The ureter has an intrinsic pacemaker that given peristalsis and modulates autonomic control of the sympathetic and parasympathetic plexus. This plexus is responsible for modulating ureteral contractions through different subtypes of adrenergic receptors α1a, α1b and α1d, which are present in the distal part of the pelvic ureter, with a higher density of α1d than other types. These receptors can be blocked by α-adrenoceptor antagonists (α-blockers), inhibiting the contraction of ureteral smooth muscle, reducing basal tone and decreasing peristaltic activity, decreasing intra-luminal pressure and increasing the pressure gradient around the stone, which aids in stone expulsion [10,11]. Several studies have demonstrated that selective α1a and α1d adrenoceptor antagonists such as tamsulosin and non-selective α-adrenoceptor antagonists such as doxazosin and alfuzosin increase stone expulsion rates and limit colicky renal pain [11–14].

Stones in the lower ureter and ureterovesical junction typically cause irritative voiding symptoms, such as increased urinary frequency, urgency and pain at the tip of the penis, which can be managed by anti-muscarinic drugs, which increase tolerability to MET [8,15].

Trospium chloride acts as a direct antagonist at muscarinic acetylcholine receptors, inhibiting smooth muscle contraction with negligible affinity for nicotinic receptors at therapeutic doses. It does not pass the blood–brain barrier, so it yields a potent localised anticholinergic effect [15–17], relieving spasms in the smooth muscles of the urinary tract. Trospium chloride is thus prescribed as a symptomatic treatment for patients with lower urinary tract symptoms (LUTS), who experience significantly greater symptoms, negative affects to quality of life (QoL), more depression, unsatisfactory sexual activity and are less productive than other groups [18].

In the present study, we evaluated the effectiveness of trospium chloride and tamsulosin as a combination therapy compared with tamsulosin alone in accelerating expulsion rates and reducing colic pain from lower ureteral stones. Although three high-quality double-blind randomised control trials failed to demonstrate significantly higher expulsion rates for MET using alfuzosin and tamsulosin, treatment with alpha blockers has been suggested by a recent meta-analysis of nine randomised controlled trials, which confirmed an overall increase in stone expulsion rates and reduced expulsion times compared to controls [19].

Al-Ansari et al. [20] reported that 0.4 mg tamsulosin produced a 21% increase in stone expulsion rates (82%), decreased stone expulsion time (6.4 days versus 9.9 days in the control group) and provided good control of colic pain (68 mg analgesic dose for the group using tamsulosin compared to a 127 mg analgesic dose for the control group). Zehri et al., [21] confirmed that 2 mg doxazosin once daily achieved an excellent expulsion rate with less need for an additional analgesic and a reduced time to stone expulsion. Dellabella et al. [22] reported that the use of tamsulosin increased stone expulsion up to 96%, and Hwang et al. [23] reported increased expulsion of lower ureteral stones with alfuzosin and methylprednisolone (up to 82%).

In our study, a higher expulsion rate and reduced expulsion time was observed with 0.4 mg tamsulosin combined with 40 mg trospium. This is likely due to the effective medication dose and double mechanism of action, which increase the tolerability of watchful waiting

and follow-up for a sufficient period without significant affects to QoL or side effects. This is in agreement with Brede et al. [24], who noticed a fourfold increase in alpha antagonist prescriptions in the emergency room with an overall decrease in cost and adverse events.

Ureteric colic is a common, painful disorder, and simple treatments that would make spontaneous stone passage more likely and quicker are still needed. In our study, we noted that patients treated with combination therapy were more comfortable and more likely to pass stones with fewer episodes of colic than patients who were treated with tamsulosin only.

Hollingsworth et al. [25] demonstrated that MET was much more likely to be chosen as a treatment for acute patients presenting to the emergency room, and only 25% of patients treated with MET required subsequent surgical intervention. However, Pickard et al. [26] provided conclusive evidence of the ineffectiveness of both tamsulosin and nifedipine in increasing the likelihood of stone passage. Nevertheless, MET is recommended clinically and is being adopted as part of routine expected management [26]. However, alternative classes of agents should be identified and trailed.

Although tamsulosin is associated with a higher incidence of dry ejaculation than trospium, in our study we found no significant difference in ejaculatory disorders between both groups. Our result may be due to the short-term period of this study and less frequent sexual behaviour of the urinary stone patients.

Conclusion

The combination of 0.4 mg tamsulosin and 40 mg trospium as MET for single lower ureteral stones <10 mm is safe and more effective than 0.4 mg tamsulosin as a mono-therapy.

Conflict of interest

We do not have conflict of interest in our study.

Source of funding

None.

References

[1] Woo HC, Jae DC, Ki HK, Young JS, Kyungseop L. Comparison and efficacy of low-dose and standard-dose tamsulosin and alfuzosin in medical expulsive therapy for lower ureteral calculi: prospective, randomized, comparative study. Korean J Urol 2012;53(5):349–54.
[2] Wood KD, Gorbachinsky I, Gutierrez J. Medical expulsive therapy. Indian J Urol 2014;30:60–4.
[3] Tzortzis V, Mamoulakis C, Rioja J, Gravas S, Michel MC, de la Rosette JJ. Medical expulsive therapy for distal ureteral stones. Drugs 2009;69(6):677–92.
[4] Seitz C, Liatsikos E, Porpiglia F, et al. Medical therapy to facilitate the passage of stones: what is the evidence? Eur Urol 2009;56(September (3)):455–71.
[5] Giannarini G, Autorino R. Recommending medical expulsive therapy for distal ureteric calculi: a step back? Eur Urol 2009;56:413–5.
[6] Snir N, Moskovitz B, Nativ O, et al. Papaverine hydrochloride for the treatment of renal colic: an old drug revisited—a prospective randomized study. J Urol 2008;179:1411–4.
[7] Finney SM, Andersson KE, Gillespie JI, Stewart LH. Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions. BJU Int 2006;98:503–7.
[8] Rovner ES. Trospium chloride in the management of overactive bladder. Drugs 2004;64(21):2433–46.
[9] Bos D, Kapoor A. Update on medical expulsive therapy for distal ureteral stones: beyond alpha-blockers. Can Urol Assoc J 2014;8:442–5.
[10] Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. J Urol 1999;162:688–90.
[11] Itoh Y, Kojima Y, Yasui T, Tozawa K, Sasaki S, Kohri K. Examination of alpha 1 adrenoceptor subtypes in the human ureter. Int J Urol 2007;14:749.
[12] Hermanns T, Sauermann P, Rufibach K, Frauenfelder T, Sulser T, Strebel RT. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomised, double-blind, placebo-controlled trial. Eur Urol 2009;56:407–12.
[13] Ahmed AA, Al-sayed AS. Tamsulosin versus alfuzosin in the treatment of patients with distal ureteral stones: prospective, randomized, comparative study. Korean J Urol 2010;51:193–7.
[14] Pedro RN, Hinck B, Hendlin K, Feia K, Canales BK, Monga M. Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. J Urol 2008;179:2244–7.
[15] Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol 2004;3:46–53.
[16] Staskin D, Kay G, Tannenbaum C, et al. Trospium chloride is undetectable in the older human central nervous system. J Am Geriatr Soc 2010;58(8):1618–9.
[17] Cardozo L, Mirone V, Gratzke C, Marberger M. Extended-release trospium chloride 60 mg—a new once-daily medication for the treatment of overactive bladder syndrome. Eur Urol Rev 2010;5(1):3–6.
[18] Koyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 2008;101:1388–95.
[19] 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.
[20] Al-Ansari A, Al-Naimi A, Alobaidy A, Assadiq K, Azmi MD, Shokeir AA. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. Urology 2010;75:4–7.
[21] Zehri AA, Ather MH, Abbas F, Biyabani SR. Preliminary study of efficacy of doxazosin as a medical expulsive therapy of distal ureteric stones in a randomized clinical trial. Urology 2010;75(June (6)):1285–8.
[22] Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. J Urol 2005;174:167–72.
[23] Hwang E, Hwang I, Yu H, et al. Effects of alfuzosin with methylprednisolone for spontaneous expulsion and pain control of lower ureteral stone. Urol Res 2012;40:605–9.
[24] Brede C, Hollingsworth JM, Faerber GJ, Taylor JS, Wolf JS. Medical expulsion therapy for ureteral calculi in the real world: targeted education increases use and improves patient outcomes. J Urol 2010;183:585–9.
[25] Hollingsworth JM, Norton EC, Kaufman SR, Smith RM, Wolf Jr JS, Hollenbeck BK. Medical expulsive therapy versus early endoscopic stone removal for acute renal colic: an instrumental variable analysis. J Urol 2013;190:882–7.
[26] 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(9991):341–9.