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The use of tamsulosin in the treatment of 10–15 mm lower ureteral stones in adults: a double-blinded randomized controlled trial

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Abstract

Background: The discovery of alpha-adrenergic receptors in the ureteral smooth muscle cells led to a thorough investigation of the therapeutic potential of alpha-blockers for ureteral calculi. Tamsulosin is a selective blocker of alpha-1A and alpha-1B adrenoceptors. It significantly improved the expulsion of distal ureteral stones measuring 3–10 mm in most randomized trials. To the best of our knowledge, tamsulosin was not tested before in the management of ureteral stones 10–15 mm. Hence, the present study aimed at estimation of the efficacy of tamsulosin in the expulsion of lower ureteral stones 10–15 mm in length compared to placebo in adult patients (primary goal) and the need for ureteral dilatation at scheduled ureteroscopy.

Methods: Between November 2017 and November 2019, 80 patients with distal ureteral stones 10–15 mm were divided into two equal groups. One group received tamsulosin 0.4 mg/day and the other received a placebo. Patients were followed-up for 8 weeks.

Results: Six patients of the tamsulosin group (15%) passed their stones spontaneously compared to none of the placebo group ($p=0.026$). Two of the 6 patients who passed the ureteral stones developed urinary retention and required endoscopic treatment of urethral stones. So, the adjusted spontaneous ureteral stone passage ratios for the tamsulosin and the control groups were 10 and 0%, respectively ($p=0.12$). Overall, 37.5% reported adverse effects in the tamsulosin group, and 30% in the placebo group ($p=0.7$). The most common adverse effect reported in both groups was dizziness, which occurred more frequently with tamsulosin (25%) than placebo (22.5%) ($p=0.9$). We noticed increased ejaculatory dysfunction among men in the tamsulosin group versus placebo group [17.9% vs. 3.5% ($p=0.1$)]. Among patients who needed ureteroscopy, ureteral dilatation was always needed in the control group versus 85.3% of the tamsulosin group ($p=0.015$). Although 23.5% of the treatment group didn't need stents after ureteroscopy compared to only 12.5% of the control group, this difference was not statistically significant ($p=0.2$).

Conclusions: Although tamsulosin significantly increased spontaneous passage of 10–15 mm lower ureteral stones in adults, it did not decrease the need for operative intervention. Preoperative tamsulosin significantly facilitated ureteral dilations during ureteroscopic management.

Keywords: Tamsulosin, Alpha-adrenergic blockers, Therapy, Ureteral calculi

1 Background

Four to fifteen percent of the world's population suffer from urolithiasis with a steadily rising incidence [1]. Twenty percent of all urinary calculi are ureteral stones, of which, 70% are located in the distal ureter [2]. Current treatment options are medical expulsive therapy (MET),

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shockwave lithotripsy, ureteroscopy, laparoscopy, and open surgery.

The discovery of α adrenergic receptors in the ureteral smooth muscle cells lead to a thorough investigation of the therapeutic potential of α-blockers for ureteral calculi [3]. Tamsulosin is a selective blocker of α-1A and α-1B adrenoceptors with some minor side effects like dizziness, drowsiness, weakness, nausea, headache, orthostatic hypotension, and retrograde ejaculation. Tamsulosin was used in the current study to represent α-blockers because it is the most studied α-blocker in the literature and the most recommended by urologic guidelines [4]. It significantly improved the expulsion of distal ureteral stones measuring 3–10 mm in most randomized trials [5]. Tamsulosin enhances the spontaneous passing of distal ureteral stones and is linked to a lower need for analgesics, a shorter hospital stay, and high patient satisfaction [6]. Hence, Tamsulosin is a non-invasive, cost-effective alternative to interventional procedures [7].

However, a multicenter placebo-controlled randomized trial, Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND), concluded that there was no difference between active and placebo treatment, or between tamsulosin and nifedipine in the expulsion of ureteral stones up to 10 mm [8]. A more recent meta-analysis of the best quality studies showed that tamsulosin significantly improves the passage of larger ureteral stones 5–10 mm [4]. Many studies tested the efficacy of tamsulosin for the expulsion of ureteral stones 5–10 mm in length, but our clinical trial is the first to test the efficacy of tamsulosin for ureteral stones 10–15 mm. Typically, patients waited for an average of 8 weeks on our waiting list for stone surgery from the diagnosis till the scheduled intervention. This study aims to test the effect of MET with tamsulosin on ureteral stones 10–15 mm during this waiting period.

2 Methods

This study was conducted in the period between November 2017 and November 2019 in an outpatient setting. Any patient with symptomatic single lower ureteral stones 10–15 mm length, 18–65 years old with normal renal function, unilateral affection, and compliance to treatment was included in the study. Patients were excluded if they met any of the following criteria: distal ureteral obstruction, solitary functioning kidney, pregnant and lactating women, ipsilateral kidney stones, abnormal ureteral and/or pelvicalyceal anatomy such as duplex system, febrile urinary tract infections, Marked hydronephrosis (society of fetal urology grade 4) [9] and contraindications of tamsulosin.

For every case, ultrasonography (USG), kidney ureter and bladder x-ray (KUB), and computed tomography of the kidney ureter and bladder (CTKUB) were done. Laboratory workup included urinalysis, and serum creatinine.

Patients were randomly divided into two groups using the closed envelope method, one group received oral tamsulosin 0.4 mg/day and the other received placebo for 8 weeks. To ensure the blindness of both the patients and the investigators, participants were given a study number and a numbered pack containing over-encapsulated medication. The research drug had to be taken once a day, at the same time every day. They also kept a diary to track the frequency of pain episodes, the date and time of passing stones, and the presence and type of medication-related side effects. Ample fluid intake was encouraged during the trial period. The study medication was discontinued at the end of follow-up, after spontaneous stone expulsion, or when intervention was indicated. The patients were followed-up weekly for 8 weeks, with urinalysis and serum creatinine measurement. Abdominal USG was done weekly while KUB and/or CTKUB were done to confirm stone expulsion or at the end of the follow-up.

Failure of therapy was defined as the absence of stone expulsion after 8 weeks. In such cases, patients underwent ureteroscopy. Failed therapy was also defined as discontinuing study medication and intervention before the completion of the study due to febrile urinary tract infections, persistent ureteral colic, or the patient's desire to shift to ureteroscopy.

The objective of this trial was the evaluation of the alpha-blocker tamsulosin as a means of MET for distal ureteral calculi 10–15 mm (primary goal), effect on the degree of hydronephrosis, analgesic requirement during follow up, its effect on the need for ureteral dilatation or stents at scheduled ureteroscopy (secondary goals). Ureteral dilatation was considered unnecessary if the 7/9.9 Fr. semi-rigid ureteroscope reached the stone easily. Double J ureteral stents were used in cases with ureteral mucosal edema, stones adherent to ureteral mucosa, or mucosal trauma during stone disintegration. Statistical analyses were done using Intercooled STATA, version 9.2. The two groups were compared regarding patient characteristics, stone criteria, and outcomes. The Mann–Whitney *U* test was used to compare continuous variables with values represented by the median and range. The Pearson chi-square or Fisher exact test were used to compare categorical variables. $p<0.05$ was considered statistically significant.

3 Results

Figure 1 shows the flowchart of the study. Forty patients in each group completed the protocol. Both groups were comparable in terms of gender distribution and other

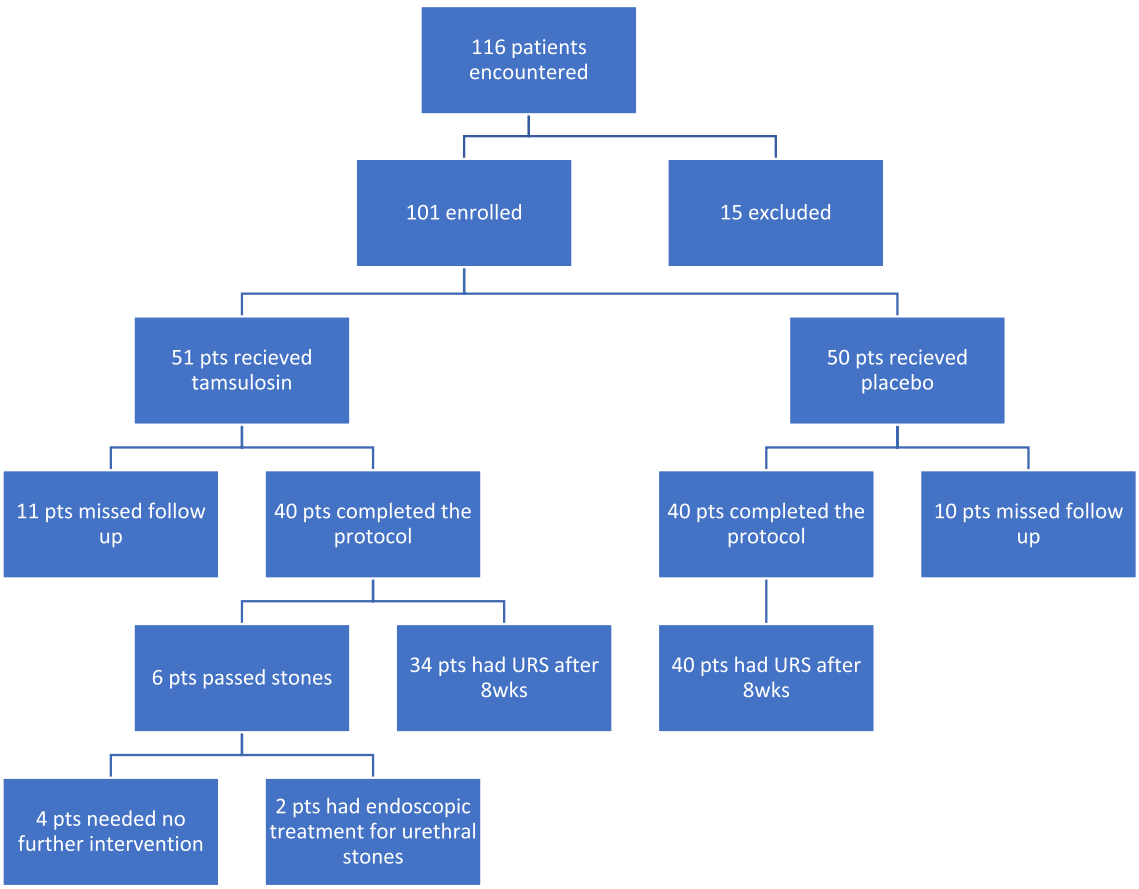

Fig. 1 The flowchart of the study

descriptive baseline characteristics. The tamsulosin group had a median age of 34.5 years, while the placebo group had a median age of 38 years ($p=0.9$). The median stone length was 11 mm (range 10–12.5) for the tamsulosin group and 10.5 mm (range 10–14) for the placebo group ($p=0.4$). Table 1 summarizes the baseline criteria of both study groups.

Six patients (15%) of the tamsulosin group passed the stones during the study period compared to none of the placebo group ($p=0.026$). Unfortunately, 2 of the 6 patients who passed the ureteral stones developed urinary retention and required endoscopic treatment of urethral stones. So, the adjusted spontaneous ureteral stone passage ratios at the end of the treatment period are 10 and 0% for the tamsulosin and the control group, respectively ($p=0.12$). The median time to expulsion was 33 days (range 20–43).

Adverse effects related to the study drug or placebo were insignificantly different between the two groups. Overall, 37.5% of the patients in the tamsulosin group suffered side effects related to the drug compared to 30% of the placebo group ($p=0.7$). The most common adverse effect reported was dizziness which occurred more frequently with tamsulosin (25%) than placebo (22.5%) ($p=0.9$). Other side effects that may or may not be attributable to the drug were reported in individual instances (sinus pressure, nosebleed, nausea, tinnitus, hands, and feet swelling). No serious adverse effects were reported in either group. Ejaculatory dysfunction, however, was more encountered among men in the tamsulosin group [5 (17.9%) vs. 1 (3.5%), ($p=0.1$)].

There was no need for parenteral analgesics. Both groups showed a decreasing need for analgesic use after the first week of treatment. An analysis of total diclofenac dosage over the 8-week treatment period (excluding the first week) showed no significant difference between both groups ($p=0.3$).

In both groups, the degree of hydronephrosis did not show any improvement in follow-up ultrasonography compared to the initial imaging studies.

Of the enrolled patients, 74 underwent ureteroscopy due to lack of stone expulsion after 8 weeks. In the control group, ureteral dilatation was always required versus 85.3% of the tamsulosin group ($p=0.015$). Fewer ureteral

Table 1 Baseline criteria of both study groups

Variable	Tamsulosin group ($N=40$)	Control group ($N=40$)	*p* value
Age median (range) years	34.5 (28, 45)	38 (29.5, 46)	0.9
Sex: *n* (%)			
Male	28 (70)	29 (72.5)	0.8
Female	12 (30)	11 (27.5)	
Laterality: *n* (%)			
Right-sided	22 (55)	24 (60)	0.7
Left-sided	18 (45)	16 (40)	
Stone length median (range) mm	11 (10–12.5)	10.5 (10–14)	0.4
Stone width median (range) mm	6 (4.5–7.5)	6 (5–8)	0.16
Radiopaque stone *n* (%)	38 (95)	37 (92.5)	0.9
Stone density median (range) HF units	1050 (720–1350)	950 (650–1250)	0.6
Degree of hydronephrosis (HN)			
n (%) No HN (SFU grade0)	8 (20)	5 (12.5)	0.4
n (%) Mild HN (SFU grade1,2)	27 (67.5)	31(77.5)	
n (%) Moderate HN (SFU grade3)	5 (12.5)	4 (10)	

SFU society of fetal urology

stents were required after ureteroscopy in the treatment group (76.5%) than in the control group (87.5%) ($p=0.2$). Table 2 summarizes both primary and secondary outcomes.

4 Discussion

In one of the first meta-analyses on MET, Hollingsworth et al. [10], combined data from 9 studies involving almost 700 patients and concluded that patients given alpha-blockers had a 54 percent higher chance of passing stones spontaneously than those who didn't receive them. They highlighted the need for high-quality randomized controlled trials to confirm the efficacy of alpha-blockers.

Based on the available evidence at the time, in 2007, the European association of urology and the American urological association (AUA) cooperative working group published a meta-analysis on MET [11]. The conclusions drawn were that alpha-blockers increase spontaneous stone passage rates and should be offered to patients.

Responding to the deficiencies in the evidence highlighted by the above studies, Pickard et al. [8] designed SUSPEND, a large, double-blind multicenter trial with a very effective concealment methodology. The primary outcome was the requirement for further treatment within 4 weeks of treatment. The study included 1167 adults with a single ureteral stone from 24 centers in the UK, were randomly assigned to tamsulosin

Table 2 Primary and secondary outcomes

Outcome	Tamsulosin group ($N=40$)	Control group ($N=40$)	*p* value
Primary outcome			
% Spontaneous ureteral stone passage	15	0	0.026
% Adjusted spontaneous stone passage	10	0	0.12
Secondary outcomes			
%Total dose of on-demand oral diclofenac ≥ 100mg[a]	72.5	65	0.3
% No dilatation on ureteroscopy	14.7[b]	0	0.015
% Stentless ureteroscopy	23.5[b]	12.5	0.2
% Overall adverse effects related to drugs	37.5	30	0.7
% Dizziness	25	22.5	0.9
% Ejaculatory dysfunction[c]	17.9	3.5	0.1

[a] Excluding the 1st week of treatment

[b] In 34 pts who underwent ureteroscopy

[c] Among men in both groups

400 mg, nifedipine 30 mg, or placebo daily for up to 4 weeks, using an algorithm with minimization covariates including the center, stone size (≤ 5 mm or > 5 mm) and stone location (upper, mid, or lower ureter). The trial was registered with the European clinical trials database, and as an international standard randomized controlled trial. The results showed no benefit from active treatment. With an adjusted risk difference of 1.3%, 80% of patients in the placebo group did not require further intervention, compared to 81% in the tamsulosin group [(95% CI 5.7–8.3); $p = 0.73$]. There was a trend towards a benefit seen with MET (including nifedipine) for stones larger than 5 mm ($p = 0.33$), and stones initially located in the lower ureter ($p = 0.099$), but neither of these was statistically significant.

Despite this high level of evidence, which contradicted the findings of the previously published meta-analyses and reviews, several concerns were raised about the study. The inclusion of stones < 5 mm, the lack of compliance confirmation, the unclear indications for intervention and the absence of radiographic confirmation of stone passage were the most notable criticisms [12, 13]. The AUA guideline panel performed a later meta-analysis including 27 studies, with a total of 1215 patients, focusing only on distal ureteral stones and excluding the SUSPEND data [14]. In the AUA guideline panel analysis, the mean number of patients per study was 45 with only 9 studies including 100 patients or more per study. There was a great variation in stone passage rates across the included studies (4–82%) [14]. This is likely a result of heterogeneity in stone sizes, as well as other factors such as variability in concomitant medications and timing of and the methods used to determine stone-free status. Their analysis showed superior stone-free rates with alpha-blockers (77.3%) compared to placebo or no treatment (54.4%) [14]. Based on such results, the guideline statement came in favor of alpha-blockers as a means of MET for uncomplicated distal ureteral stones ≤ 10 mm [14]. A later Cochrane database systematic review by Campshroer et al. [15] supported such statement. They also performed subgroup analysis dividing such stones into two groups according to size (≤ 5 mm and 6–10 mm). Their results showed minimal or no effect for alpha-blockers on stone clearance for stones 5 mm or less and a substantial effect on stones 6–10 mm [15]. The same conclusions were outlined by Aboumarzouk et al. [16] in their meta-analysis which included 60 randomized trials with more than 9500 patients. Our findings conform to the conclusions of the aforementioned analyses regarding spontaneous ureteral stone passage with an attempt to increase the stone size limit that could respond to MET with tamsulosin.

Unfortunately, all those years of study with enormous numbers of trials and patients did not lead to a unanimous decision about MET with alpha-blockers. A recent meta-analysis by Yu et al. [17] included 8 placebo-controlled trials with 2284 patients showed no benefit of MET with alpha-blockers over placebo as regards stone expulsion. They didn't do the subgroup analysis that stratifies the stones into two groups (≤ 5 mm and 6-10 mm), the analysis that yielded a remarkable alpha-blocker effect on the expulsion of the larger stone group according to several studies [7, 15, 16].

4.1 Secondary outcome

Several investigators examined the effect of alpha-blockers on pain during the treatment period with various indicators like the number of pain episodes [15, 18], the total dose of diclofenac [15] or readmission to the hospital due to pain [16]. There is nearly a consensus that patients experience less pain with alpha-blockers than with placebo. Our results contradict such agreement as we found an insignificant difference between the two study groups regarding the total dose of diclofenac. This contradiction may be explained by the exclusion of diclofenac doses received during the first week of treatment. The reason for that is to make sure that the doses received to treat the pain at first presentation (which is not covered by the effect of the alpha-blocker) are excluded.

Alsaikhan et al. [19] investigated the facilitatory effect of preoperative alpha-blockers on ureteroscopy in their meta-analysis that included 12 RCTs with 1352 patients. They found a significantly less need for dilatation, more likelihood of surgeons reaching the stones, shorter operative times, and more stone-free patients at follow-up. In their RCT, Koo et al. [20] focused on the effect of alpha-blockers on the force needed to insert an access sheath and ureteral mucosal injury. They found significantly less maximal insertion forces and less ureteral trauma with alpha-blockers. We spotted a significantly less need for dilatation during ureteroscopy when tamsulosin was used compared to placebo (85.3 vs. 100%) despite no effect on the degree of hydronephrosis or the need for stent placement after ureteroscopy. Such conclusions derived from ureteroscopy sessions support the idea of extending the cut-off stone size treated with alpha-blockers as patients may benefit from either spontaneous stone passage or facilitation of ureteroscopy.

The side effect profile of alpha-blockers remains a valid concern. There have been concerns about their hypotensive effect, especially at the initiation of treatment, in the elderly, and those on concomitant vasodilator drugs [16]. Furthermore, ejaculatory dysfunction is very bothersome to men. Tamsulosin is

also associated with intraoperative floppy iris syndrome, an important risk factor for complications during cataract surgery [16]. The present study showed no significant difference between tamsulosin and placebo regarding overall reported side effects, dizziness, or ejaculatory dysfunction. Nevertheless, it should be noted, and patients must be told that its use as MET is still "off-label", and there is no safety data for its use in women.

To the best of our knowledge, the present study is the first RCT for large lower ureteral stones 10–15 mm. It showed that although tamsulosin may facilitate the passage of such stones, the overall need for intervention did not decrease. Furthermore, the facilitation of ureteroscopy was another advantage of tamsulosin.

The present study has several strengths, including double-blinding design, only lower ureteral stones enrolled, no stone < 10 mm, longer duration of therapy (2 months), and inclusion of ureteroscopy data. The limitations of our study are the small number of patients which was derived from a rather forgiving sample size calculation, the lack of CONSORT statement, the methodology is not population-based, the compliance with medications was patient-reported, other alpha-blocker drugs were not studied, stone volume was not calculated, and ureteroscopies were done by multiple surgeons.

5 Conclusions

The present study shows that the indications of MET with the alpha-blocker tamsulosin can be extended to include distal ureteral stones 10–15 mm. The results highlight the possible benefit of tamsulosin in facilitating ureteral dilatation during ureteroscopic management of such stones. Further studies with a larger number of patients are required to consolidate such indications of the drug and to investigate its ability to decrease the requirement of endoscopic treatment for this group of calculi.

Abbreviations

AUA: American urological association; CTKUB: Computed tomography of the kidney, ureter, and bladder; KUB: Kidney, ureter, and bladder plain X-ray; MET: Medical expulsive therapy; RCT: Randomized controlled trial; SFU: Society of fetal urology; SUSPEND: Spontaneous urinary stone passage enabled by drugs; USG: Ultrasonography.

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Author contributions

MS: conception and design of the work and final revision of the manuscript. ME: acquisition, analysis, and interpretation of the data. AE: conception and design of the work and interpretation of the data. MA: Interpretation of the data and revision of the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the "research ethics committee" of the Faculty of Medicine, Assiut University, Assiut, Egypt. Registration Number: 17100966. The trial was registered in the "good clinical practice network" clinical trial registry https://ichgcp.net/clinical-trials-registry/NCT03274700. Every participant signed an informed consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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