Tamsulosin to treat uncomplicated distal ureteral calculi: a double blind randomized placebo-controlled trial

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ABDEL-MEGUID TA, TAYIB A, AL-SAYYAD A. Tamsulosin to treat uncomplicated distal ureteral calculi: a double-blind randomized placebo-controlled trial. The Canadian Journal of Urology. 2010;17(3):5178-5183.

Purpose: *To evaluate efficacy and outcome of tamsulosin therapy for 4 mm-10 mm uncomplicated distal ureteral stones.*

Materials and methods: *A total of 150 patients (adults with newly diagnosed single unilateral distal ureteral 4 mm-10 mm stones) were double blindly randomized into GA or GB. All patients received traditional treatment of hydration and analgesia as needed. Additionally, patients received either placebo (GA) or 0.4 mg tamsulosin (GB) oral tablets once daily. Treatment and follow up were continued for up to 4 weeks. Endpoints were spontaneous stone passage rates (SPR) and passage time for different stone sizes within 4 weeks study period.*

Results: *Analysis included 75 patients, in each group, with comparable characteristics. Overall SPR was 56% in GA and 81.3% in GB; achieving significant absolute risk reduction (ARR = 25.3%; $p < 0.01$) and number needed to treat (NNT) of 3.95. SPR for stones ≤ 6 mm was 69.2% in GA versus 90.7% in GB (ARR = 21.5%, $p < 0.01$). For stones 7 mm-10 mm, SPR was 26.1% in GA and 57.1% in GB (ARR = 31.0%, $p < 0.01$). NNT for ≤ 6 mm and 7 mm-10 mm stones was 4.65 and 3.23, respectively ($p < 0.05$). Median time for passage of ≤ 6 mm stones was 17 versus 9 days in GA and GB; while for 7 mm-10 mm stones it was 20 versus 15 days, respectively. During the first two weeks, 77.8% of ≤ 6 mm stones in GB have passed versus 23.8% of 7 mm-10 mm stones. Analgesia consumption was significantly less in GB ($p < 0.01$). No significant adverse effects were observed.*

Conclusions: *Tamsulosin therapy for uncomplicated distal ureteral calculi augments SPR, shortens passage time and decrease need for analgesia. Particularly, tamsulosin shortens the passage time for smaller stones, and augments the passage rate for larger stones.*

Key Words: ureter, adrenergic alpha-antagonists, tamsulosin, urinary calculi

Introduction

Urinary stones are the third most common affliction of the urinary tract,[1] with estimated prevalence of 2%-3% and life time recurrence rate of approximately 50%.[2,3] Although not risk free, extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) are accepted as first choice for ureteral stone management.[4] Nevertheless, small distal ureteral stones demonstrate high probability of spontaneous passage, with an estimate of 68% of ureteral stones ≤ 5 mm, and 47% of stones between 5 mm-10 mm would pass spontaneously.[4]

In light of prevalence of urinary stones, high recurrence rates, associated risk of ESWL and URS, as well as high spontaneous stone passage rates (SPR) of small distal ureteral calculi; a medical therapy that might promote spontaneous passage would be an appealing approach.[5-10]

Accepted for publication March 2010

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Identification of α1-adrenoreceptor (AR) subtypes[6,7] responsible for ureteral muscular tone and contractions, directed the evaluation of pharmacological interventions aimed at promoting stone passage. Blocking α1-AR action and promoting muscle relaxation is the basis of medical expulsive therapy for ureteral stones to facilitate stone passage and reduce its associated pain.[8-10] Medical treatment with tamsulosin, a selective α1A-α1D AR, has proved to be safe and effective as demonstrated by the increased stone expulsion rate, reduced expulsion time and reduced need for analgesia in patients treated with tamsulosin.[9,10]

The current double-blind randomized controlled trial (RCT) prospectively evaluated the efficacy and outcome of tamsulosin as a medical therapy for uncomplicated distal ureteral stones. To the best of our knowledge, using tamsulosin, this is the first double-blind RCT reporting on weekly SPRs based on different stone sizes.

Materials and methods

Setting

The study was conducted in the author's institution from June 2008 to December 2009. The study protocol was approved by the ethics committee and written informed consent was obtained from each patient.

Study population

Inclusion criteria were adults over 18 years old, of either sex with single, unilateral, newly diagnosed, 4 mm-10 mm in transverse diameter, distal ureteral stones; in paired kidneys patients with minimal or no epsilateral hydronephrosis, normal contralateral kidney and normal overall renal functions. Stones evident in either KUB x-ray or ultrasonography or both were selected, to allow for follow up. Exclusion criteria were patients with history of epsilateral ureteral endoscopic or surgical manipulations or ESWL; patients with symptomatic urinary tract infections; pregnant or lactating ladies; patients already receiving alpha blockers, beta blockers, calcium channel antagonists or corticosteroids; and patients with serious medical conditions. Patients who refused randomization or lost to follow up during the study period were excluded as well, Figure 1.

Study design

At baseline, irrespective to age or sex, patients were allocated randomly in 1:1 ratio into either group A (control) or B (treatment) using sealed envelopes. Both treating physicians and patients were blinded to randomization. Patients of both groups received the traditional treatment of hydration and analgesia (diclofenac 100 mg) as needed.

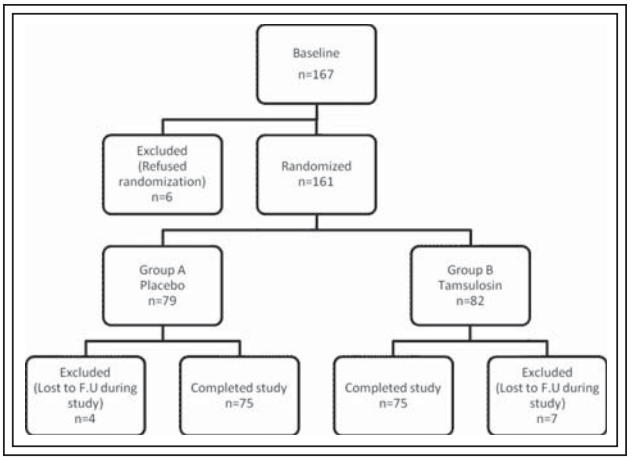

Figure 1. Patients randomization and exclusions.

Additionally, patients of group A received placebo, while group B received 0.4 mg tamsulosin oral tablets once daily. Patients with non-symptomatic urinary tract infections were given appropriate antibiotics. Subjects received the treatments and continued their follow up for a maximum of 4 weeks; or until earlier spontaneous passage of the stone or withdrawal from the study to convert to interventional treatment modality before the end of the allotted 4 weeks duration.

Baseline assessment and follow up

Baseline assessment included non-contrast spiral CT for initial diagnosis and measuring stone size. KUB x-ray and ultrasonography were done initially and on weekly follow ups. Non-contrast spiral CT was repeated at the end of study to confirm stone status.

Endpoints

The primary endpoint of the study was to determine SPRs for different stone sizes within the 4 weeks study period. Secondary endpoints included determination of stone passage time (time needed for spontaneous stone passage), weekly stone passage rate, episodes of renal colics, need for analgesia, need to convert to interventional treatment such as ESWL or ureteroscopic stone manipulation, and drug adverse effects. The endpoints were analyzed according to stone size, whether ≤ 6 mm or 7 mm-10 mm stones.

Statistical analysis was performed using SPSS 11.0 software (SPSS, Inc., Chicago, Illinois). Discrete variables are presented as counts or frequencies and were evaluated by the chi-square test. The Mann-Whitney U test was used to determine the median. Comparison among groups was performed using analysis of variance (ANOVA), $p < 0.05$ was considered as statistically significant.

TABLE 1. **Patients randomization and exclusions**

Stone size/ location	Group A n/total (%)	Group B n/total (%)
≤ 6 mm	52/75 (69.3%)	54/75 (72.0%)
7 mm-10 mm	23/75 (30.7%)	21/75 (28.0%)
Rt. juxtavesical	16/75 (21.3%)	20/75 (26.7%)
Rt. intramural	13/75 (17.3%)	14/75 (18.7%)
Lt. juxtavesical	31/75 (41.3%)	23/75 (30.7%)
Lt. intramural	15/75 (20.0%)	18/75 (24.0%)

Results

At baseline, 167 patients matched the inclusion criteria, Figure 1, 17 patients were excluded due to not accepting randomization (6) and loss to follow up during study period (4 in group A and 7 in group B). The study analysis involved a total of 150 patients, 75 patients in each group, with comparable population characteristics of sex, age and stone sizes ($p < 0.05$). Group A involved 53 males and 22 females, compared to 50 males and 25 females in group B. The age ranged between 19-72 yrs (median = 36) in group A; and 20-67 yrs (median = 34) in group B. The stones sized 4 mm-10 mm in both groups (median = 6 mm in group A and 5 mm in group B). Group A incorporated 52 patients having ≤ 6 mm stones and 23 patients with 7 mm-10 mm stones; while group B enclosed 54 and 21 patients with ≤ 6 mm and 7 mm-10 mm stones, respectively. Stones locations are shown in Table 1.

Spontaneous passage, Table 2, was attained in a total of 42/75 (56%) in group A and 61/75 (81.3%) in group B; to achieve a significant absolute risk reduction (ARR) for retaining stones (ARR = 25.3%; $p < 0.01$) and number needed to treat to benefit (NNT) of 3.95. For stones ≤ 6 mm, SPR was 69.2% (36/52) in group A versus 90.7% (49/54) in group B (ARR = 21.5%, $p < 0.01$). For larger stones (7 mm-10 mm), SPR was 26.1% (6/23) in group A, in contrast to 57.1% (12/21) in group B (ARR = 31.0%, $p < 0.01$). As exhibited in Table 2, the difference between relative risk reduction (RRR) for ≤ 6 mm versus that of 7 mm-10 mm stones is statistically significant ($p < 0.01$), in favor of smaller stones (RRR = 69.9%and 42%, respectively). However, there is statistically significant difference ($p < 0.05$) between NNTs for ≤ 6 mm and 7 mm-10 mm stones, favoring larger stones (NNT = 4.65 and 3.23, respectively).

The median time for passage of stones ≤ 6 mm was 17 days (range 3-25) in group A, and 9 days (range 2-22) in group B. For 7 mm-10 mm stones, median time for passage was 20 (range 9-27) and 15 days (range 8-24) in groups A and B, respectively. Over individual consecutive weeks, for all stone sizes (4 mm-10 mm), the stone passage rate reached its peak 16/75 (21.3%) during the third week in group A, while it reached an earlier and higher peak 34/75 (45.3%) during the second week in group B, Table 3. In the treatment group, 77.8% of ≤ 6 mm stones have passed during the first 2 weeks of treatment while only additional 13% have passed during the last 2 weeks of treatment. On the other hand, in the same group, 23.8% of 7 mm-10 mm stones have passed during the first 2 weeks with additional 33.3% has passed during the last 2 weeks of treatment.

The need for oral analgesia was evident in group A as compared to group B. Analgesics consumption was diclofenac 100 mg tablets; 6-12 (median = 9) in group A versus 2-8 (median = 4) in group B ($p < 0.01$). Episodes of renal colics were reported in 58/75 (77.3%) in group A and in 20/75 (26.7%) in group B ($p < 0.05$). All patients who experienced renal colics were treated on an ER basis with intramuscular diclofenac, except five patients who needed urgent hospitalization and intervention. All patients tolerated the medication well with no significant adverse effects. Five male patients reported decreased seminal volume, though none of them discontinued the medication.

A total of 47/150 (31.3%) patients in both groups failed to pass their stones. Of them, 34 were treated by either ureteroscopy (26) or ESWL (8); whereas

TABLE 2. **Spontaneous stone passage rates and risk of retaining stones in both groups with different stone sizes by 4 weeks duration**

	Spontaneous passage		ARR	RRR	NNT
	Group A	Group B			
≤ 6 mm	36/52 (69.2%)	49/54 (90.7%)	21.5%	69.9%	4.65
7 mm-10 mm	6/23 (26.1%)	12/21 (57.1%)	31.0%	42%	3.23
4 mm-10 mm	42/75 (56.0%)	61/75 (81.3%)	25.3%	57.5%	3.95

ARR = absolute risk reduction; RRR = relative risk reduction; NNT = number needed to treat

TABLE 3. **Weekly stone passage rates according to the size**

Duration	Stone size	Group A n/total (%)	Group B n/total (%)
1st week	≤ 6 mm	7/52 (13.5%)	12/54 (22.2%)
	7 mm-10 mm	1/23 (4.3%)	1/21 (4.8%)
	4 mm-10 mm	8/75 (10.7%)	13/75 (17.3%)
2nd week	≤ 6 mm	7/52 (13.5%)	30/54 (55.6%)
	7 mm-10 mm	2/23 (8.7%)	4/21 (19.0%)
	4 mm-10 mm	9/75 (12.0%)	34/75 (45.3%)
3rd week	≤ 6 mm	14/52 (26.9%)	6/54 (11.1%)
	7 mm-10 mm	2/23 (8.7%)	5/21 (23.8%)
	4 mm-10 mm	16/75 (21.3%)	11/75 (14.7%)
4th week	≤ 6 mm	8/52 (15.4%)	1/54 (1.9%)
	7 mm-10 mm	1/23 (4.3%)	2/21 (9.5%)
	4 mm-10 mm	9/75 (12.0%)	3/75 (4.0%)

four patients passed their stones while awaiting for intervention and nine patients lost to follow up after the end of study.

Discussion

Depending on stone size and location, a substantial portion is able to pass the ureter spontaneously. However, this process may take days to weeks with need for analgesics.[11] A passage rate of 25%, 45% and 70% for proximal, mid and distal ureteral stones ≤ 7 mm, respectively, was reported.[12] Ueno et al[13] evaluated more than 500 patients and reported a spontaneous stone expulsion rate of 57% for 5 mm calculi. Kinder et al[14] focused on lower ureteral calculi and calculated a 94% frequency of passage of stones ≤ 5 mm and 45% for calculi > 5 mm. The AUA meta-analysis[15] of distal ureteral stones found that stones < 5 mm passed spontaneously with a rate of 71% to 100%, whereas stones from 5 mm-10 mm passed with a rate of 25% to 46%. Time to spontaneous passage similarly depends on stone size and location. Time to passage of distal ureteral stones was reported in AUA meta-analysis[15] to be 8, 12, and 22 days for stones sized ≤ 2 mm, 3 mm, and 4 mm-6 mm, respectively. In further study,[16] the mean passage time was between 5 days (for smaller distal stones) and 59 days (for larger proximal stones), indicating that watchful waiting strategy of 4 to 6 weeks may be reasonable for smaller distal stones if the patient remains asymptomatic and uncomplicated.

Watchful waiting approach for ureteral stones has recently been augmented by using pharmacological therapy, which can reduce symptoms and facilitate stone expulsion. Therapy includes analgesics, anti-inflammatory drugs, corticosteroids, calcium channel antagonists and alpha-blockers.[8,9,17-25] The use of alpha-blockers was proposed based on the evidence that alpha-ARs have an important role in lower ureteral physiology.[5-7] De Sio and coworkers[21] demonstrated that addition of tamsulosin to standard medical therapy significantly increased the expulsion rate and decreased expulsion time. Stone expulsion rate was 90.0% in tamsulosin arm and 58.7% in standard therapy arm; with a mean stone expulsion time of 4.4 versus 7.5 day, respectively. The addition of tamsulosin resulted in lower use of analgesics and fewer hospitalizations for recurrent colic. Results from systematic reviews[4,26,27] further provide evidence for a higher stone expulsion rate and a reduced time to expulsion using alpha-blockers compared to a standard therapy or placebo control group. In a meta-analysis[26] of 691 patients in nine RCTs using calcium channel blockers or alpha-blockers for stones sized 3.9 mm to 7.8 mm; there is an overall 65% greater likelihood of stone passage in treated patients. The meta-analysis demonstrated the positive impact of nifedipine is marginal and alpha-blockers are superior to nifedipine and, hence, may be the preferred agents for medical therapy. Additionally, in another meta-analysis,[4] nifedipine yielded an estimate of 75% SPR while alpha-blockers yielded 81% SPR. Compared to control, the meta-analysis also showed an absolute increase in SPR of 9% for nifedipine, which was not statistically significant; and 29% for alpha-blockers, which was statistically significant. Steroids do provide a slight added benefit, but do not appear to be as important as alpha or calcium channel blockers.[22,24] However, there is current reappraisal of the role of alpha-blockers in

management of distal ureteric calculi.[25,28] In a well-conducted RCT,[25] the authors assessed in a double-blind fashion the efficacy and safety of tamsulosin therapy versus placebo for distal ureteric calculi ≤ 7 mm in size. Notably, expulsion rate and time to expulsion were comparable in the two arms.

The current study focused on adult patients with symptomatic uncomplicated single newly diagnosed distal ureteral calculi of 4 mm-10 mm size. The sample-size in the current study (75 patients in each group) is larger than the calculated sample-size (50 patients in each group) in previous RCT with similar design.[25] Due to the fact that the distal ureter presents the highest concentration of α1-AR,[5-7] tamsulosin was elected as a treatment for those patients. We planned to limit the maximum treatment and follow up period to 4 weeks because conservative management within 4 to 6 weeks appears to be reasonable[15,16] and longer durations can increase complication rates by up to 20%.[29]

In this study, for stones sized 4 mm-10 mm, SPR attained in treatment group shows both statistical and clinical significance compared to control group, with an ARR of 25.3% and RRR of 57.5%. Additionally, the NNT of 3.95 substantiates the efficacy and clinical significance of tamsulosin treatment, meaning that for every 3.95 patients with distal ureteral calculi ≤ 10 mm, treatment with tamsulosin for up to 4 weeks can avert the inconvenience of intervention in one extra patient, compared to non-treated patients. Moreover, significant ARRs (21.5% and 31.0%) were noted in treatment group for ≤ 6 mm and 7 mm-10 mm calculi, respectively. Consequently, the clinical significance of treatment which is demonstrated with NNT of 4.65 and 3.23 for stones sized ≤ 6 mm and 7 mm-10 mm, respectively, favors better clinical efficacy in larger stones. However, comparing the RRR for ≤ 6 mm (69.9%) to that for 7 mm-10 mm stones (42%), the difference is statistically significant in favor of small sized stones, making RRR appears more impressive for smaller stones. This finding can be explained by the lower risk for retaining smaller stones compared to larger stones in the control group.

As far as the time needed for stone passage, regardless of stone size, we observed that SPR reached its peak (21.3%) during the third week in control group, while it reached an earlier and higher peak (45.3%) during the second week in tamsulosin group. Smaller stones (≤ 6 mm) passed earlier and required shorter period of treatment, since 77.8% of these stones passed within 2 weeks of tamsulosin treatment. In contrast, for larger stones (7 mm-10 mm), only 23.8% of calculi could pass during the first 2 weeks and additional 2 weeks of treatment were needed to achieve the maximum effect (57.1%). Given that smaller stones are more likely to pass than larger ones, it is reasonable to conjecture that the impact of tamsulosin therapy will be relatively earlier on smaller stones.

The reduced need for oral analgesia and fewer episodes of renal colics in treatment group further highlight the beneficial effect of tamsulosin. Since stones that fail to pass spontaneously will ultimately require some sort of intervention such as ureteroscopy or ESWL, boosting SPR by tamsulosin will consequently circumvent the inconvenience of such intervention in many patients.

Study limitations

The study was conducted in a single center. Only recently diagnosed stones were elected which may not reflect the entire representation of stones. A larger scale multicenter double-blind RCT, including impacted stones need to be undertaken to provide better evidence in this regard.

Conclusions

Tamsulosin is an effective and safe therapy for uncomplicated distal ureteral calculi. Tamsulosin augments spontaneous stone passage and shortens time to passage for stones sized 4 mm-10 mm. Particularly, tamsulosin shortens the passage time for smaller stones, and augments the passage rate for larger stones. Reduced analgesia requirements, minimal adverse effects and decreased need for intervention are additional advantages of tamsulosin therapy. □

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