
A Comparative Study between Tamsulosin and Doxazosin for Management of Lower Ureteral Stones

*Bahir Abdul- Razzaq Mshemish MSc, PhD**

Abstract

Background: recent studies have reported excellent results with medical expulsive therapy (MET) for lower ureteral calculi, both in terms of stone expulsion and control of ureteral colic pain.

Objective: Aim of this study was to compare the efficacy and safety of tamsulosin and doxazosin as a medical expulsive therapy for symptomatic, uncomplicated lower ureteral stones.

Patients and Methods: one hundred patients with lower ureteral stones of ≤ 10 mm were randomly divided into 3 groups, where 33 patients received tamsulosin 0.4 mg daily (group I); 33 patients received doxazosin 4 mg daily (group II), and 34 patients were considered as control group (group III) as did not receive tamsulosin or doxazosin. All groups received meloxicam regularly for one week and then on demand. Follow up was done on a weekly basis for 45 days.

Results: stone size mean was comparable in the three groups (6.17 ± 3.44 , 6.25 ± 2.93 , and 5.97 ± 4.11 mm; respectively for groups I, II, and III). Stone expulsion rate was 82%, 76%, and 47% in groups I, II, and III, respectively. The difference in expulsion rate for groups I and II with respect to group III was significant ($p < 0.05$). Mean expulsion time for groups I, II, and III was 7.87 ± 6.43 , 8.12 ± 5.67 , and 15.23 ± 7.21 days, respectively. The expulsion time was significantly shorter in groups I and II than in group III ($p < 0.05$). Patients taking tamsulosin and doxazosin had fewer pain attacks than did group III patients (1.14 ± 0.32 , 1.32 ± 0.43 vs. 2.16 ± 0.52). Emergency room visits was nil for all patient groups and only 3 cases of drug side effects, one in group I and two in group II, were recorded.

Conclusion: using of tamsulosin or doxazosin for medical treatment of lower ureteric stones is safe and effective. Tamsulosin did not have any significant benefits over doxazosin.

Keywords: tamsulosin, doxazosin, lower ureteral stone.

Introduction

Ureteral stones are a common medical problem. They account 1:5 of urolithiasis and two-third is located in the lower third of the ureters. Conservative medical treatment for ureteral stones should be applied first. Extracorporeal shock wave lithotripsy (ESWL) or ureteroscopy can be utilized when conservative treatment is failed [1]. Stone location and size are the most important factors in predicting the probability of spontaneous stone passage [2]. Spontaneous expulsion occurs in 1/4 to 1/2 of cases for lower ureteral stones of 5 to 10 mm diameter [3].

The watchful waiting approach is supported by using pharmacologic therapy, which can reduce complications and facilitate stone expulsion. These complications involve infection of the urinary tract, hydronephrosis, and renal dysfunction [4]. Successful medical expulsive therapies (MET) can be achieved by anti-inflammatory/anti-edematous treatment with glucocorticoids and by relaxation of ureteral smooth muscle with α -blockers or calcium channel blockers. For these tested drugs; the resulting findings for number of randomized clinical trials almost always been interpreted as proof of efficacy [5].

The α_1 receptors have three subtypes, namely: α_{1a} , α_{1b} , and α_{1d} . Among these, α_{1d} receptors have the highest density in the lower ureters [6]. Blockade of α_1 receptors inhibits basal tone, reduces peristaltic amplitude and frequency of ureteral contraction, and decreases intra-luminal pressure while increasing the rate of fluid transport and induce an increase in the intra-ureteral pressure gradient around the stone that helps in stone expulsion [7].

Because of its uroselectivity for α_{1a} and α_{1d} ; excellent tolerability; and the lack of need for dose

titration, tamsulosin was the most commonly used α -blocker as a medical expulsive therapy. However, limited comparative studies indicate that other α -blocker agents can be similarly effective [8,9].

The objective of this trial was to evaluate the efficacy and safety of tamsulosin and doxazosin as a medical expulsive therapy for treatment of lower ureteral stones.

Patients and Methods

A prospective single-blind randomized controlled study was conducted in the Department of Urology /Al-Sadeer Hospital with subjects in an outpatient setting with acute renal colic from January to May 2011. Lower ureteral stones were diagnosed on the basis of plain abdominal X-rays, ultrasonography, and computed tomography when necessary. Additionally, the patients underwent a series of measurements, including case history, physical examination, complete blood cell count, routine urinalysis, and serum creatinine measurement.

All male and female patients ≥ 18 yr presenting with acute renal colic were evaluated for study participation. Patients with a single ureteral stone ≤ 10 mm below the common iliac vessels were eligible for the study. Exclusion criteria were the presence of multiple ureteral stones; hydronephrosis; renal dysfunction; urinary tract infection; a solitary kidney; pregnancy; a history of ureteral surgery or previous endoscopic procedures; hypersensitivity to α -blocker; current α -blocker, calcium-antagonist or corticosteroid medication; and contraindications for NSAIDs.

A total of 105 patients with lower ureteral stones were randomly divided into 3 groups and given

medications for 45 days. They received a first treatment of meloxicam injection (15 mg) by intramuscular injection, with a second dose after 30 minutes if necessary, to relief acute renal colic. For ethical considerations, all patients in the 3 groups received high fluid intake with meloxicam tablets (7.5 mg) every 12 hours for 1 week and then meloxicam injection (15 mg) as needed, up to a maximum of 2 times per day. Patients in group I (n=35) received a daily oral dose of tamsulosin (0.4 mg), group II patients (n=35) received a daily oral dose of doxazosin (4 mg), while group III (n=35) received meloxicam only (control group).

The study medications were discontinued after spontaneous stone expulsion (primary endpoint), intervention, or at the end of the study period. Successful results were defined as complete stone passage and failure was considered if the patient failed to pass the stone at the end of study period; uncontrolled pain; adverse events; or uroseptic fever leading to hospitalization. In these cases, and to achieve ethical requirements, ureterorenoscopy or ESWL was performed.

The follow-up was performed weekly with urinalysis, serum creatinine measurement, abdominal ultrasonography, and, in radiopaque stones, plain abdominal x-ray. Also, patients were asked if they had seen any stone passage during urination. Abdominal CT was performed for patients with radiolucent stones if the stone was not expelled by the end of study. For patients with stone-free ureters on final imaging study but unnoticed stone expulsion, the date of last positive stone status was recorded.

The efficacy of treatment was evaluated in terms of rate (proportion of patients experiencing stone expulsion, as a primary endpoint), time of stone passage, frequency of pain attacks, and complications of the medication (as a secondary endpoint).

This study was planned to have a size that would be sufficient to detect any significant difference among patient groups. Data were expressed as proportions (number or percentage of patients) or mean $\pm$ standard error of means (SEM).

Excel program of Microsoft office 2007 was applied where student's t-test, analysis of variance (ANOVA) and chi-square (X^2 analysis) were used to statistically analyze the parameters of stone size, expulsion rate, time to expulsion, pain attacks, and side effects. In the exploratory analysis of the endpoints, all p -values <0.05 considered significant.

Results

From 105 patients initially enrolled, 100 patients completed this study (group I=33; group II=33; and group III=34). There was no statistically significant

difference among the 3 groups in terms of sex, age, stone side, size and location ($p>0.05$). The baseline characteristics of patient groups are summarized in table (1).

Regarding rate of stone expulsion at the end of study, a significant statistical difference was noted between groups I (82%), II (76%) vs. group III (47%) ($p<0.05$). Whereas; no significant difference was recorded between group I and II ($p>0.05$). For stones ≤ 5 mm size, no statistically significant differences were observed in the expulsion rate among the three groups (96%, 92%, and 89%, respectively) ($p>0.05$), while for stones >5 mm size, a significant statistical difference was noted between groups I (75%), II (69%) vs. group III (31%) ($p<0.05$), whereas no significant difference was recorded between groups I and II ($p>0.05$), table (2).

Concerning the mean time of expulsion, a significant statistical difference was noted between groups I (7.87 ± 6.43 days), II (8.12 ± 5.67 days) vs. group III (15.23 ± 7.21 days) ($p<0.05$), whereas no significant difference was recorded between groups I and II ($p>0.05$). In addition, no statistical difference ($p>0.05$) was observed among the mean sizes of the expelled stones in the three groups after the end of medical therapies (6.46 ± 2.63 , 6.18 ± 1.99 , and 5.86 ± 1.75 mm, respectively) (table 2).

Ureteroscopy or extracorporeal shock wave lithotripsy (ESWL) were scheduled for patients who did not subsequently expel the stone. While awaiting intervention, three patients in group I and two patients in group II expelled their stones spontaneously (2,4,7,3 and 6 days after termination of therapy, respectively), whereas no spontaneous expulsion of the stone was recorded in group III.

Patients taking tamsulosin or doxazosin had fewer pain attacks than did patients in the control group, where a significant statistical difference was noted between groups I (1.14 ± 0.32), II (1.32 ± 0.43) vs. group III (2.16 ± 0.52) ($p<0.05$), whereas no significant difference was recorded between groups I and II ($p>0.05$), as shown in table (2).

Hospitalization with consecutive intervention and discontinuation of the medication due to uncontrollable pain occurred in 7 patients: 2 patients (6%) in group I, 2 patients (6%) in group II, and 3 patients (9%) in group III. However, the difference was not statistically significant ($p>0.05$) and emergency room visits was nil for all patient groups.

No serious adverse drug reactions were recorded in the three groups. Just 1 patient (3%) in group I recorded retrograde ejaculation and 2 patients (6%) in group II recorded an episode of hypotension, which did not require suspension of the therapy (table 2).

Table (1): Baseline characteristics of the patient groups.

Variables	Tamsulosin gr. (n=33)	Doxazosin gr. (n=33)	Control gr. (n=34)	<i>p</i> -value I vs. II, I vs. III, and II vs. III
Sex (male/female)	23/10	21/12	24/10	$p>0.05$
Mean age (years)	44.3±12.5	45.1±11.6	43.8±13.2	$p>0.05$
Stone side (right/left)	17/16	16/17	18/16	$p>0.05$
Stone size mean (mm)	6.17±3.44	6.25±2.93	5.97±4.11	$p>0.05$
Size ≤ 5mm, no. (%)	13 (39%)	15 (45%)	14 (41%)	$p>0.05$
Size > 5mm, no. (%)	20 (61%)	18 (55%)	20 (59%)	$p>0.05$
Distal site no. (%)	22 (67%)	24 (73%)	25 (74%)	$p>0.05$
Ureterovesical junction site no. (%)	11 (33%)	9 (27%)	9 (26%)	$p>0.05$

Note: there was no statistically significant difference ($p>0.05$) among our patient groups in their baseline characteristics.

I: represent tamsulosin group.

II: represent doxazosin group.

III: represent control group.

Table (2): Expulsion rates, pain attacks, hospital readmission, and complications.

Variables	Tamsulosin gr. (n=33)	Doxazosin gr. (n=33)	Control gr. (n=34)
Expulsion rate, no. (%)	27 (82) ^a	25 (76) ^a	16 (47) ^b
Expulsion rate for stones ≤5 mm, no. (%)	32 (96) ^a	30 (92) ^a	30 (89) ^a
Expulsion rate for stones >5 mm, no. (%)	25 (75) ^a	23 (69) ^a	11 (31) ^b
Mean time of expulsion (days)	7.87±6.43 ^a	8.12±5.67 ^a	15.23±7.21 ^b
Mean size of expelled stone (mm)	6.46±2.63 ^a	6.18±1.99 ^a	5.86±1.75 ^a
Mean no. of pain episodes	1.14±0.32 ^a	1.32±0.43 ^a	2.16±0.52 ^b
Hospitalization no. (%)	2 (6) ^a	2 (6) ^a	3 (9) ^a
Emergency room visits	Nil	nil	nil
Adverse reactions no. (%)	1 (3)	2 (6)	nil

Results with non identical superscript letters (a, b) within the three patient groups considered significantly differ at $p < 0.05$.

Discussion

Advances in endo-urolological techniques and instrumentation have largely diverted the management of ureteral stones by open surgeries to the minimal invasive methods like ESWL and ureterorenoscopic removal of stones^[10].

Nevertheless, these techniques are not risk-free, quite expensive, and not widely available in the developing countries. Therefore, many doctors demonstrated that the patient should simply be observed to see if the stone will pass without treatment^[5].

Watchful waiting is appropriate for small stones that are not causing acute symptoms and likely to pass spontaneously, although it may occur at the expense of some discomfort to the patient^[2]. Spontaneous passage depends upon stone size, shape, location and associated ureteral edema. Ureteral calculi 4-5 mm in size have a 40-50% chance of spontaneous passage. In contrast, calculi >6 mm have less than 5% chance of spontaneous passage within a 6 weeks period^[3,5].

During the last few years, there is a great deal for using of adjuvant pharmacologic intervention to increase the expulsion rate and to reduce pain

attacks and analgesic consumption when a conservative therapy is considered. Calcium channel blockers, corticosteroids, and α -blockers are extensively studied and used as a medical expulsive therapy for lower ureteric stones^[11-14].

The α_{1a} and α_{1d} adrenergic receptors are present more densely in the distal third of ureters than other adrenergic receptors.

When stimulated, they inhibit the basal tone, peristaltic wave frequency and the ureteral contractions.

The α_1 antagonists may work on the obstructed ureters by inducing an increase in the intraureteral pressure gradient around the stone, that is, an increase in the urine bolus above the stone, thereby increasing the chance of stone expulsion^[6,7].

Several studies demonstrated a favorable benefit of α_1 -blockers in facilitating stone passage, increasing the rate of stone expulsion, and decreasing pain and analgesic use. Cervenakov *et al* concluded that the treatment by α_1 -blockers considerably decreased not only lower urinary tract symptoms, but also helped to accelerate the passing of minor calculi from the terminal parts of the ureters of 80.4% of patients^[15].

Dellabella *et al* used tamsulosin as a spasmolytic drug during episodes of ureteral colic due to juxtavesical calculi, observed an increased stone expulsion rate with a decrease in stone expulsion time, the need for hospitalization and endoscopic procedures, and provided particularly good control of colic pain ^[16]. De Sio *et al* found that patients taking tamsulosin achieved significantly higher rates of distal ureteral stone passage (90%) over a shorter time (4.4 days). They also had lower analgesic use and fewer hospitalizations ^[17].

Agrawal *et al* study failed to show any statistically significant differences between tamsulosin and alfuzosin regarding stone expulsion rate, expulsion time, or need for analgesic therapy ^[8]. Pedro *et al* concluded that alfuzosin improves the patient discomfort associated with stone passage and decreases the time to distal ureteral stone passage but does not increase the rate of spontaneous stone passage (77.1% for placebo and 73.5% for alfuzosin, $p=0.83$) ^[18].

Results of the present study confirmed the efficacy of α -blockers for lower ureteric stones. A total of 82% of patients taking tamsulosin and 76% of patients taking doxazosin were able to expel their stones at the end of study compared with 47% of patients taking only analgesic (table 2).

Patients taking tamsulosin and doxazosin expelled the stones in significantly fewer days. Tamsulosin and doxazosin also decreased the frequency of pain attacks associated with stone passage. No significant difference ($p > 0.05$) was observed among the 3 groups in the number of hospital readmission and emergency room visits was nil for all groups, where tamsulosin did not have any significant benefits over doxazosin (table 2).

Regarding α -blocker trials with mean stone sizes ≤ 5 mm, only few studies demonstrated a significantly higher expulsion rate in the treatment group ^[19,20].

In contrast, with trials investigating the efficacy with mean stone sizes > 5 mm; most of the studies demonstrated a significant benefit in stone expulsion rates ^[21].

A maximum observation period of 45 days was chosen because a longer period can increase the complication rate by more than 20% ^[22].

In the present study and for stones ≤ 5 mm in size, the expulsion rate was 96%, 92% and 89% in group I, II, and III, respectively. No statistically significant differences were observed among the 3 groups ($p > 0.05$). For stones > 5 mm in size, the expulsion rate was 75%, 69% and 31% in group I, II, and III, respectively.

A significant statistical difference was noted between group I and III ($p < 0.05$) and between group II and III ($p < 0.05$), whereas no significant difference was recorded between group I and II ($p > 0.05$), as shown in table (2). Regarding the expulsion rate, we hypothesize that tamsulosin and doxazosin are of

more value in treatment of lower ureteric stones > 5 mm size than in treatment of stones ≤ 5 mm in size.

As a secondary endpoint, number of pain episodes was significantly different between study and control arms (table 2).

Patients in the tamsulosin and doxazosin arms required fewer analgesics until stone expulsion (as number of pain episodes was fewer) than patients in the control arm. This difference may be attributable to the accelerated stone expulsion with a consecutive shorter time at risk for painful events. Additionally, a true analgesic effect of α -blockers have been reported ^[5].

The most frequently reported adverse events with α -blockers were transient hypotension and retrograde ejaculation ^[20]. Pedro *et al* reported 12% adverse events in the α -blocker group compared with 0% in the placebo group ^[18], whereas Yilmaz *et al* and Liatsikos *et al* reported no serious adverse events ^[9,21].

In the present study, minor therapy-related side effects were observed in 3 patients as shown in table-2 (one patient taking tamsulosin developed retrograde ejaculation and two patients taking doxazosin developed an episode of hypotension).

The 3 patients were able to complete the study. No patient developed serious side effects during this study.

We believe that further studies using larger groups are needed to confirm these findings of α -blockers and to evaluate the effect of different variables such as age, sex, body mass index, laterality, location and other sizes of the ureteral stone on the expulsion rate.

Conclusion

We can conclude that MET should be considered for uncomplicated lower ureteral calculi before ureteroscopy or ESWL.

Tamsulosin and doxazosin have been found to be safe and increase stone expulsion rates, decrease acute attacks by acting as a spasmolytic, reduces mean days to stone expulsion and, consequently, decreases analgesic dose usage.

Patients taking tamsulosin did not have any significant benefits over those taking doxazosin. However, using α -blockers requires larger, multicentre trials before their application can be universally recommended.

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* Department of Pharmacotherapy-College of Pharmacy / AL- Mustansiriyah University
Mobile: (+9647702581925)
E-mail:bahiralkinani@yahoo.com