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Urolithiasis

Tamsulosin versus Alfuzosin in the Treatment of Patients with Distal Ureteral Stones: Prospective, Randomized, Comparative Study

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Purpose: We evaluated and compared the efficacy of tamsulosin and alfuzosin in the medical treatment of symptomatic, uncomplicated distal ureteral stones.

Materials and Methods: A total of 87 patients with distal ureteral stones of ≤10 mm were randomly divided into 3 groups. Group I patients (n=29) received 0.4 mg tamsulosin daily, group II patients (n=30) received 10 mg alfuzosin daily, and group III patients (n=28) were not given tamsulosin or alfuzosin. Patients in all groups received Diclofenac sodium regularly for 1 week and then on demand. Follow-up was done on a weekly basis for 30 days.

Results: The mean stone size was comparable in the 3 groups (4.97±2.24, 5.47±2.13, and 5.39±1.81 mm, respectively). The stone expulsion rate was 86.2%, 76.6%, and 50% in groups I, II, and III, respectively. The difference in groups I and II with respect to group III was significant (p=0.0028 and 0.035). The mean expulsion time for groups I to III was 7.52±7.06, 8.26±7.34, and 13.90±6.99 days, respectively. The expulsion time was significantly shorter in groups I and II than in group III (p=0.0097 and 0.026). Patients taking tamsulosin and alfuzosin had fewer pain attacks than did group III patients (1.24±0.57 vs. 1.43±0.67 vs. 1.75±1.17). Only 3 cases of drug side effects, 2 in group I and 1 in group II, were recorded.

Conclusions: The use of tamsulosin or alfuzosin for the medical treatment of lower ureteric stones proved to be safe and effective. Moreover, tamsulosin did not have any significant benefits over alfuzosin.

Key Words: *Urinary calculi; Ureter; Alfuzosin; Tamsulosin*

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INTRODUCTION

Urolithiasis is a health problem of worldwide importance. Ureteral stones account for 20% of urolithiasis, and 70% of ureteral stones are located in the lower third of the ureter. It is generally believed that conservative medical treatment for ureteral stones should be applied first (which is also the wish of most patients). If conservative treatment is unsuccessful, shock wave lithotripsy (SWL) or ureteroscopy (URS) can then be utilized [1]. The most important factors in predicting the likelihood of spontaneous stone passage are stone location and stone size [2]. For distal ureteral stones of 5 and 10 mm diameter, spontaneous expulsion occurs in 25% to 53% of cases [3].

The simple watchful waiting approach can result in complications, however, such as infection of the urinary tract, hydronephrosis, and renal function effects [4]. Therefore, the watchful waiting approach is extended by using pharmacologic therapy, which can reduce symptoms and facilitate stone expulsion. One possible pathway for medical treatment is anti-inflammatory and anti-edematous treatment by glucocorticoids. Another option is the relaxation of ureteral smooth muscle, e.g., by α1-adrenoceptor antagonists (α-blockers) or calcium channel blockers. A number of randomized clinical trials have tested these drugs, and the resulting findings have almost always been interpreted as proof of efficacy [5].

The rationale behind the use of alpha blockers is that stimulation of the α1 receptors in the ureter increases the force of ureteral contraction and the frequency of ureteral

peristalsis. Thus, blockade of α1 receptors inhibits basal tone, reduces peristaltic amplitude and frequency, and decreases intra-luminal pressure while increasing the rate of fluid transport. Alpha-1 blockers also induce an increase in the intra-ureteral pressure gradient around the stone that helps in stone expulsion [6]. Three subtypes of α1 receptor have been described, namely, α1a, α1b, and α1d. Among these, α1d receptors have the highest density in the distal ureter [7].

Tamsulosin is the most commonly used α-blocker for the medical treatment of ureteric stones because of its excellent tolerability; the lack of need for dose titration upon initiation of treatment, which allows a fully effective dose to be administered right away; and its uroselectivity for α1a and α1d, resulting in relaxation of the smooth muscles of the lower ureter, facilitation of stone passage, and relieving of pain. However, limited direct comparative data indicate that other α-blockers such as alfuzosin, doxazosin, and terazosin can be similarly effective [8,9].

The main aim of this prospective study was to present our experience with the efficacy of tamsulosin and alfuzosin in the medical treatment of symptomatic, uncomplicated distal ureteral stones.

MATERIALS AND METHODS

Patients presenting at the emergency department or urology clinic at our institution with acute renal colic were evaluated for study participation in a prospective manner between March 2008 and November 2009. Distal ureteral stones were diagnosed on the basis of plain abdominal X-rays, urinary ultrasonography, and helical 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. The lower ureter was defined as the segment from the lower border of the sacroiliac joint to the vesico-ureteric junction. Patients ≥18 years of age with a single, unilateral ureteral stone of ≤10 mm were eligible for the study. Patients were excluded if they met any of the following criteria: (1) age less than 18 years, (2) pregnant or lactating women, (3) history of previous surgery on the ipsilateral ureter, (4) stone more than 10 mm, (5) multiple stones, (6) bilateral ureteric stones, (7) solitary kidney, (8) urinary tract infection, (9) moderate or severe hydronephrosis, (10) currently on α-blocker therapy, (11) known allergy to tamsulosin or alfuzosin, (12) contraindications for nonsteroidal anti-inflammatory agents (e.g., gastritis), or (13) renal insufficiency. All patients received a first treatment of Diclofenac 75 mg by intramuscular injection, with a second dose after 30 minutes if necessary. If Diclofenac gave inadequate pain relief, Tramal hydrochloride 100 mg by intramuscular injection was given. If the pain was resolved, the patient was dismissed and automatically enrolled in the study after providing informed written consent. The study protocol was approved by the ethics committee of our hospital.

A total of 90 patients with distal ureteral stones ≤10 mm in diameter were randomly divided into 3 equal groups and given medications for 30 days. All patients in the 3 groups received diclofenac sodium (50 mg, tablet) every 12 hours for 1 week and then Diclofenac sodium injection (75 mg, amp) as needed, up to a maximum of 2 times per day. Patients in group I (n=30) received a daily oral dose of tamsulosin (0.4 mg), patients in group II (n=30) received a daily oral dose of alfuzosin (10 mg), and patients in group III (n=30) received Diclofenac sodium only. The study medications were discontinued after spontaneous stone expulsion, intervention, or at the end of the study period. Absences of stone expulsion at the end of the study or intervention before the end of the study as the result of uncontrollable pain or adverse events were considered failed therapy.

Follow-up visits were performed on a weekly basis. At the follow-up visit, every patient underwent urine analysis, serum creatinine measurement, a plain X-ray KUB, and abdominal ultrasonography. 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 expulsed by the end of study. For patients with a stone-free ureter on the last 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 and time of stone passage, frequency of pain attacks, and complications of medications.

1. Statistical analysis

Statistical analyses were performed with Student's t-test, ANOVA, chi-square, and Fisher's exact test by using the parameters of stone size, expulsion rate, time to expulsion, pain attacks, and side effects. The power used was 0.80, and the level of significance was 5%.

RESULTS

A total of 90 patients were enrolled in the study, and 87 patients completed the study (1 patient from group I and 2 patients from group III dropped out). Group I (29 patients) consisted of 19 men and 10 women (mean age: 40.7±14.8 years), group II (30 patients) consisted of 18 men and 12 women (mean age: 41.1±15.2 years), and group III (28 patients) consisted of 19 men and 9 women (mean age: 38.9±13.3 years). The mean stone size was 4.97±2.24 mm for group I, 5.47±2.13 mm for group II, and 5.39±1.81 mm for group III. There were no statistically significant differences between the 3 groups in terms of sex, age, or stone size ($p > 0.05$). The baseline characteristics of the studied patients are summarized in Table 1.

The results of the data analysis showed that 25 of 29 cases in group I (86.2%), 23 of 30 in group II (76.7%), and 14 of 28 in group III (50%) expelled the stones by the end of the study. A significant statistical difference was noted between groups I and III (p=0.0028) and between groups II

TABLE 1. Baseline characteristics of the studied patients

Variables	Group I (n=29)	Group II (n=30)	Group III (n=28)	p-value
	Tamsulosin group	Alfuzosin group	Control group	
No. of patients	29	30	28	ns
Mean age (years)	40.7±14.8	41.1±15.2	38.9±13.3	ns
Sex (male:female)	1.5:1	1.9:1	2.1:1	ns
Stone size (mm)	4.97±2.24	5.47±2.13	5.39±1.81	ns
Stone side right/left	13/16	16/14	15/13	–

ns: non-significant

TABLE 2. Expulsion rates, pain attacks, hospital readmission, and complications

Variables	Group I (n=29)	Group II (n=30)	Group III (n=28)	p-value
	Tamsulosin group	Alfuzosin group	Control group	
Stone expulsion rate at 30 days, no (%)	25 (86.2)	23 (76.7)	14 (50)	0.0028 group I vs. III 0.035 group II vs. III
Expulsion rate for stone ≤5 mm (%)	89.5	88.2	73.3	ns
Expulsion rate for stone >5 mm (%)	70	61.5	23.1	0.024 group I vs. III 0.049 group II vs. III
Expulsed stone size (mm)	4.76±2.31	5.04±1.92	4.43±1.22	ns
Time of stone expulsion (days)	7.52±7.06	8.26±7.34	13.9±6.99	0.0097 group I vs. III 0.026 group II vs. III
No. of pain attacks	1.24±0.57	1.43±0.67	1.75±1.17	0.042 group I vs. III
Hospital readmission, no (%)	1 (3.4)	2 (6.6)	4 (14.3)	ns
Overall complications	2 (6.9)	1 (3.3)	0 (0)	ns

ns: non-significant

and III (p=0.035), whereas no significant difference was recorded between groups I and II (p=0.36). The mean size of the expulsed stones after the medical therapies was 4.76±2.31 mm in group I, 5.04±1.92 mm in group II, and 4.43±1.22 mm in group III. No statistical difference was observed between the mean sizes of the expulsed stones in the 3 groups ($p > 0.05$).

For stones ≤5 mm size, the expulsion rate was 89.5% of cases in group I, 88.2% in group II, and 73.3% in group III. No statistically significant differences were observed between the 3 groups ($p > 0.05$). For stones >5 mm size, the expulsion rate was 70% of cases in group I, 61.5% in group II, and 23.1% in group III. A significant statistical difference was noted between groups I and III (p=0.024) and between groups II and III (p=0.049), whereas no significant difference was recorded between groups I and II (p=0.69).

The mean time to expulsion was 7.52±7.06 days (range, 3-26 days) in group I, 8.26±7.34 days (range, 3-27 days) in group II, and 13.9±6.99 days (range, 5-27 days) in group III. A significant statistical difference was noted between groups I and III (p=0.0097) and between groups II and III (p=0.026), whereas no significant difference was recorded between groups I and II (p=0.72).

Patients who did not subsequently expel the stone were scheduled for ureteroscopy or extracorporeal shock wave lithotripsy (ESWL). While awaiting intervention, 2 patients in group I and 1 patient in group II expelled their stones spontaneously (3, 9, and 7 days after therapy, respectively), whereas no spontaneous expulsion of the stone was recorded in group III.

Patients taking tamsulosin had fewer pain attacks than did patients in the other 2 groups (the mean number of pain attacks was 1.24±0.57 for group I patients, 1.43±0.67 for group II patients, and 1.75±1.17 for group III patients). A significant statistical difference was registered only between groups I and group III (p=0.042). There was no significant difference in the number of pain attacks between patients in group I and group II (p=0.25) or between patients in group II and group III (p=0.21).

No severe complications were recorded in the 3 groups. Two patients (6.9%) in group I recorded retrograde ejaculation and 1 patient (3.3%) in group II recorded an episode of hypotension, which did not require suspension of the therapy. Hospital readmissions with consecutive intervention and discontinuation of the medication due to uncontrollable pain occurred in 7 patients: 1 patient (3.4%) in group I, 2 patients (6.6%) in group II, and 4 patients (14.3%) in group III. The difference was not statistically significant ($p > 0.05$) (Table 2).

DISCUSSION

A variety of treatment options are available for the management of distal ureteral stones, including open ureter-

olithotomy, ureteroscopic stone extraction, and shock wave lithotripsy. However, some argue that the patient should simply be observed to see if the stone will pass without treatment. The literature provides a variety of results regarding spontaneous ureteral stone passage. Ueno et al evaluated more than 500 patients and reported a spontaneous stone expulsion rate of 57% for 5 mm calculi [4]. Kinder et al reported a 94% spontaneous expulsion rate for stones ≤5 mm and a 45% rate for calculi greater than that size [10].

The decision for conservative medical treatment or active interventional treatment is not based only on the overall probability of stone expulsion. For many patients, factors such as time for convalescence or reexposure to dreaded colics during conservative treatment make a considerable impact on the decision to opt for an interventional treatment.

There is currently a great deal of enthusiasm for adjuvant pharmacologic intervention to increase the expulsion rate and to reduce pain attacks and analgesic consumption when a conservative therapy is considered. The drugs generally used in medical expulsive therapies for lower ureteric stones are calcium channel blockers, α-blockers, and corticosteroids [11-14].

Most studies demonstrated a favorable benefit to tamsulosin and alfuzosin in facilitating stone passage, increasing the rate of stone expulsion, and decreasing pain and analgesic use, with only a few studies failing to find statistically significant differences between patients using and not using these drugs.

Cervenakov et al in a randomized study registered a significant statistical difference in the stone expulsion rate between the group treated with tamsulosin and the control group [15]. Similar results were reported in a study by Dellabella et al [16].

De Sio et al published a study of 96 patients with distal ureteral stones to test the efficacy of tamsulosin as a medical expulsive therapy and found that patients taking tamsulosin achieved significantly higher rates of stone passage (90%) over a shorter time period (4.4 days) [17]. They also had lower analgesic use and fewer hospitalizations.

In a double-blinded placebo-controlled trial conducted by Pedro et al [18] on 76 patients to test the efficacy of alfuzosin as a medical expulsive therapy for distal ureteral stones, the authors 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). In contrast, Agrawal et al recently published a placebo-controlled study of 102 patients with distal ureteral stones to compare the efficacy of alfuzosin and tamsulosin in the management of lower ureteral stones [8]. Patients were classified into 3 equal groups. Group 1 patients (n=34) received 0.4 mg tamsulosin daily, group 2 patients (n=34) received 10 mg alfuzosin daily, and group 3 patients (n=34) received placebo (control group). Stone expulsion was observed in 82.3% in group 1, 70.5% in group 2, and 35.2% in group 3. The average expulsion time for groups 1, 2, and 3 was 12.3, 14.5, and 24.5 days, respectively. The results of both study groups (groups 1 and 2) were superior to those of the placebo group (p=0.003 and p=0.001, respectively). The study failed to show any statistically significant differences between tamsulosin and alfuzosin regarding stone expulsion rate, expulsion time, or need for analgesic therapy.

In trials investigating the effecacy of α-blockers on ureteral stone expulsion with mean stone sizes <5 mm, only a few studies demonstrated a significantly higher expulsion rate in the treatment group [19,20]. In contrast, regarding α-blocker trials with stone sizes ≥5 mm, most of the studies demonstrated a significant benefit in stone expulsion rates [21].

The present study was designed to compare and test the effectiveness of tamsulosin and alfuzosin on the management of distal ureteric stones. Patients receiving tamsulosin or alfuzosin were compared with patients receiving analgesic only as a control. The study was limited to patients with stone sizes of ≤10 mm. A maximum observation period of 30 days was chosen because a longer period can increase the complication rate by 20% [22].

Our results confirmed the efficacy of tamsulosin and alfuzosin for distal ureteric stones. A total of 86.2% of patients taking tamsulosin and 76.7% of patients taking alfuzosin were able to expel their stones at the end of study compared with 50% of patients taking only analgesic. Patients taking tamsulosin and alfuzosin expelled the stones in significantly fewer days. Tamsulosin and alfuzosin also decreased the frequency of pain attacks associated with stone passage. Tamsulosin did not have any significant benefits over alfuzosin.

For stones ≤5 mm in size, the expulsion rate was 89.5 of cases in group I, 88.2% in group II, and 73.3% in group III. No statistically significant differences were observed between the 3 groups (p>0.05). For stones >5 mm in size, the expulsion rate was 70% of cases in group I, 61.5% in group II, and 23.1% in group III. A significant statistical difference was noted between groups I and III (p=0.024) and between groups II and III (p=0.049), whereas no significant difference was recorded between groups I and II (p=0.69).

Regarding the expulsion rate, we hypothesize that tamsulosin and alfuzosin are of more value in the treatment of distal ureteric stones >5 mm size than in the treatment of stones ≤5 mm in size. We believe that further studies using larger groups are needed to confirm these findings and to evaluate the effect on the stone expulsion rate of different variables such as age, sex, body mass index, laterality, location of the stone, and size of the stone . Thus, we advocate the need for multicentre trials.

The most frequently reported adverse event with tamsulosin was transient hypotension [20]. No significant difference in adverse events was noted between tamsulosin 0.4 mg and 0.2 mg. Pedro et al reported 12% adverse events in the alfuzosin 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 (2 patients taking tamsulosin developed retrograde ejaculation and 1 patient taking alfuzosin developed an episode of hypotension). The 3 patients were able to complete the study. No patients developed serious side effects during the study period.

CONCLUSIONS

The use of tamsulosin and alfuzosin as a medical expulsive therapy for distal ureteric stones proved to be safe and effective as demonstrated by the increased stone expulsion rate, decreased expulsion time, and reduced pain attacks. Moreover, patients taking tamsulosin did not have any significant benefits over patients taking alfuzosin. These drugs can be safely used for the management of uncomplicated distal ureteral stones before undertaking any invasive intervention.

Conflicts of Interest

The authors have nothing to disclose.

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