Role of Tamsulosin in Clearance of Upper Ureteral Calculi After Extracorporeal Shock Wave Lithotripsy
A Randomized Controlled Trial

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Purpose: To evaluate the role of tamsulosin in stone clearance in patients with upper ureteral stone after extracorporeal shock wave lithotripsy (SWL).
Materials and Methods: This randomized controlled trial was performed on 117 patients with a single upper ureteral calculus undergoing SWL. The study group received 0.4 mg tamsulosin daily while the control group received hydration and analgesic on demand for a maximum of 3 months. Follow-up visits were performed at 1, 2, and 3 months after SWL. Efficiency of tamsulosin was evaluated in terms of success rate, time for expulsion of fragments, number of SWL sessions, incidence of steinstrasse, and pain intensity.
Results: The clearance rate after 1, 2, and 3 months were higher in tamsulosin group than the control group (85%, 89.8%, and 91.5% versus 70.6%, 79.3%, and 86.2%; $P = .01$, $P = .11$, and $P = .34$, respectively). The mean time for expulsion of the fragments was 26.78 ± 11.96 days and 31.28 ± 18.31 days in tamsulosin and control groups, respectively ($P = .138$). Steinstrasse developed in 8 patients in tamsulosin group and in 13 patients in control group ($P = .167$). Visual analogue scale pain score was 24.92 ± 7.57 in tamsulosin group and 41.81 ± 17.24 in control group ($P = .000$).
Conclusion: Tamsulosin helps in clearance of upper ureteral stones after 1 month of SWL, particularly stones with size of 11 to 15 mm with less requirement of SWL sessions and analgesics.

Keywords: extracorporeal shockwave lithotripsy, tamsulosin, calculi, randomized controlled trial

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INTRODUCTION

Symptomatic ureteral calculi represent the most common condition encountered by a urologist in an emergency setting.[1] In the presence of normal renal function and absence of infection, observation is generally preferred for ureteral calculi with a maximum of 5 mm diameter.[2] Intervention is recommended for individuals with larger stones, especially greater than 5 mm.[3] Extracorporeal shock wave lithotripsy (SWL) or retrograde endoscopic stone removal comprises the next line of management depending on the stone location and size, urgency of clearance, and patient's preference.[2] Extracorporeal shock wave lithotripsy has been recommended as a first-line treatment modality for upper ureteral calculi in several studies with a success rate of 80% to 90%.[4-6]

Recently, medical expulsion therapy (MET) has shown encouraging results in facilitating spontaneous clearance of lower ureteral calculi as well as fragments after SWL for renal and/or ureteral calculi.[7-11] Tamsulosin, an $\alpha 1_A$-adrenoceptor blocker, has been used in several recent MET experiments, but the results of studies are variable and most of them are being carried out on patients with lower ureteral calculi.[12-14] However, study on upper ureteral calculi is scarce. Therefore, whether tamsulosin administration for patients with upper ureteral stones would improve the stone-free rate as the stone size increases is still under debate. A prospective randomized trial was thus planned to evaluate and compare the effects of tamsulosin administration after SWL in patients with upper ureteral calculi of different sizes.

MATERIALS AND METHODS

A prospective randomized controlled trial was conducted at our institute between January 2006 and June 2008 on outpatient department basis. The study protocol was approved by Institutional Review Board and a written informed consent was obtained from each patient.

Hundred and twenty patients in the age range of 18 to 70 years with symptomatic, unilateral, and solitary upper ureteral calculi proved on plain abdominal kidney, ureter, and bladder (KUB) radiography and ultrasonography of the kidney, ranging from 6 to 15 mm in major axis were included in this study. Upper ureter was defined as part of the ureter between the pelvi-ureteral junction and the sacroiliac joint. Exclusion criteria were as follows: active urinary tract infection, fever, acute renal failure, chronic renal failure, history of urinary tract surgery or endoscopic treatment, uncorrected distal obstruction, severe hydronephrosis, pregnancy, concomitant treatment with α blockers, calcium channel blockers, or steroids, morbid obesity (BMI >30), or history of previous failed SWL.

Prior to study, complete blood count, blood level of urea, serum level of creatinine, urine analysis, urine culture, KUB x-ray after preparation, and ultrasonography of the KUB region were carried out on all the patients.

Patients were randomly divided into 2 groups, A and B. Randomization was done by using sealed envelope technique by the Junior House officer and all the patients were evaluated by the doctor who was blinded to the treatment given. Patients in group A received tamsulosin 0.4 mg once a day, just before the session of SWL for 3 months or until the clearance of calculi, which was earlier. Patients in group B did not receive tamsulosin or any other medication to facilitate expulsion of stone after SWL.

All the patients underwent SWL in supine position with electro magnetic lithotripter (HK–ESWL–VI Shenzhen, China) at 12 to 15KV. Stone localization was done using C-arm. In a single session, maximum of 3000 shock waves were given. All patients were advised to take 2500 cc fluid daily, and analgesic diclofenac was on demand during the study period.

Repeated sessions of SWL were given for an incomplete fragmented calculus every 3 weeks. The patient was termed as SWL failure when incomplete or no fragmentation was found after three sessions. Patients were evaluated for stone clearance, time to stone clearance, number of SWL sessions, pain intensity, incidence of steinstrasse, and any side effects at 1, 2, and 3 months. At each follow-up, KUB x-ray, ultrasonography of KUB, urine analysis as well as measurement of blood level of urea and serum level of creatinine were performed.

Successful results were defined as complete stone clearance or presence of less than a 3-mm clinically insignificant and asymptomatic residual calculus. Those who did not complete the follow-up without clearance were excluded from the study. Unsuccessful patients underwent ureteroscopy as an auxiliary procedure.

The primary outcome of this study was the success rate, and the secondary outcomes were clearance time, sessions required for clearance, pain intensity, and incidence of steinstrasse.

Eventually, 117 patients were available for final analysis. Statistical analysis was performed by SPSS (the Statistical Package for the Social Sciences, Version 13.0, SPSS Inc., Chicago, Illinois, USA) software, using Chi-square test,

Fisher's exact test, and student's *t* test. *P* values less than .05 were considered statistically significant.

RESULTS

Both groups were comparable in demographic profile (Table 1). The clearance rate after 1, 2, and 3 months of follow-up were higher in tamsulosin group than the control group (85%, 89.8%, and 91.53% versus 70.69%, 79.3%, and 86.21%; $P = .01$, $P = .11$, and $P = .34$, respectively) and the difference was statistically significant ($P = .01$) at 1 month, but not at 2 and 3 months ($P > .05$).

Stone Clearance Stratified By the Size of Stone (Table 2)

Stone size of 6 to 10 mm

The clearance rate after 1, 2, and 3 months was higher in tamsulosin group than the control group (90%, 93%, and 93% versus 87%, 90%, and 90%, respectively) and the difference was statistically insignificant ($P = .68$).

Stone size of 11 to 15 mm

The clearance rate after 1, 2 and 3 months was higher in tamsulosin group than the control group (79.3%, 86.2%, and 90% versus 53.5%, 67.8%, and 82%, respectively) and the difference was statistically significant at 1 month ($P = .039$), but not at 2 and 3 months ($P = .09$ and $P = .4$).

Stone Clearance Stratified by Gender

There was no statistically significant difference in stone clearance between men and women in both groups ($P > .05$) (Table 3).

The median value of SWL sessions was 1 and 2 in tamsulosin and control groups, respectively, and the difference was statistically significant ($P = .031$) (Table 4). The frequency of SWL sessions was also compared between tamsulosin and control groups by chi-square test and a statistically significant difference was found $P = .034$.

The mean time for expulsion of the fragments was 26.78 ± 11.96 days in tamsulosin group and 31.28 ± 18.31 days in the control group, and difference was statistically insignificant ($P = .138$) (Table 4).

Steinstrasse developed in 8 patients in tamsulosin

Table 1. Demographic and clinical characteristics of study groups

	Tamsulosin group (n = 59)	Control group (n = 58)
Mean patients' age, y	32.20 ± 12.22	36 ± 13.78
Gender, male/female	44/15	41/17
Stone size, mm		
6 to 10 mm	30	30
11 to 15 mm	29	28

Table 2. Stone clearance stratified by size of stone at 1, 2, and 3 months

Stone size	1 month			2 months			3 months		
mm	Tamsulosin Group	Control group	*P*	Tamsulosin Group	Control group	*P*	Tamsulosin Group	Control group	*P*
6 to 10	27 (90%)	26 (87%)	.68	28 (93%)	27 (90%)	.64	28 (93%)	27 (90%)	.64
11 to 15	23 (79.3%)	15 (53.5%)	.039	25 (86.2%)	19 (67.8%)	.09	26 (90%)	23 (82%)	.4
Overall (6 to 15)	50 (85%)	41 (70.69%)	.01	53 (89.8%)	46 (79.3%)	.1	54 (91.53%)	50 (86.21%)	.35

Table 3. Stone clearance stratified by gender at 1, 2, and 3 months

Stone size	Gender	1 Month		2 Months		3 Months	
		Tamsulosin Group	Control Group	Tamsulosin Group	Control Group	Tamsulosin Group	Control Group
6 to 15 mm	Male	37/44 (84%)	29/41 (71%)	39/44 (89%)	32/41 (78%)	40/44 (91%)	35/41 (85%)
	Female	13/15 (87%)	12/17 (71%)	14/15 (93%)	14/17 (82%)	14/15 (93%)	15/17 (88%)
	P	.588	.613	.518	.507	.624	.568

Table 4. Secondary outcome analysis

	Tamsulosin group	Control group	*P*
Mean expulsion time, d	26.78 ± 11.96	31.28 ± 18.31	.138
Median value of extracorporeal shock wave lithotripsy sessions	1	2	.031
Number of Steinstrasse	8	13	.167
Visual analogue scale pain score	24.92 ± 7.57	41.81 ± 17.24	.000

group and in 13 patients in the control group and difference was statistically insignificant ($P = .167$) (Table 4). All of these patients had stones in the range of 11 to 15 mm. Six patients were treated conservatively in tamsulosin group and passed the stone while 2 patients required ureteroscopic stone removal (URS) as an auxiliary procedure. Of 13 patients in the control group, 5 required auxiliary treatment (URS) and 8 patients passed the fragment by conservative treatment.

Visual analogue scale pain score in tamsulosin and control groups were 24.92 ± 7.57 and 41.81 ± 17.24, respectively, and difference was statistically significant ($P = .000$) (Table 4).

DISCUSSION

Extracorporeal shock wave lithotripsy and flexible URS remain the first-line treatment option for patients with upper ureteral calculi measuring < 1.5 cm.[2] Despite more number of auxiliary procedures associated with SWL, its completely noninvasive nature makes it an attractive first choice.[15] After SWL, the final clearance of the fragment from the ureter is akin to the spontaneous passage of ureteral calculi. The fragment size is an important factor that determines the passage of stone through the ureterovesical junction, the narrowest part of the ureter.[10] Spasm, edema, or infection may hinder stone passage.[16,17] Ureteral colic, associated with stone, is the manifestation of the visceral pain that refers to the somatic region corresponding to the spinal segment of the sympathetic supply of the ureter.[17] Increased intraluminal pressure due to calculus obstruction and increased lactic acid production resulting from smooth muscle spasm may have parts in this event.[18]

Watchful waiting strategy is appropriate for small stones that are not causing acute symptoms and are likely to pass spontaneously.[19] Ureteral calculi 4 to 5 mm in size have a 40% to 50% chance of spontaneous passage. In contrast, calculi greater than 6 mm have a less than 5% chance of spontaneous passage. Majority of the stones that pass do so within a 6-week period after the onset of symptoms.[20]

Numerous studies have recently demonstrated promising results in increasing expulsion rate with the addition of drugs for MET, including corticosteroid, glyceryl trinitrate, prostaglandin synthesis inhibitors, calcium channel blockers, and α-adrenoceptor blocker. Treatment with a calcium channel blocker or an α blocker are suggested by recent meta analysis of nine randomized controlled trials showing that both of these METs improve the spontaneous expulsion rate of small ureteral stones by 65% obviating the need for surgical treatment.[7]

Alpha adrenergic receptors are found in abundance in the detrusor and intramural part of the ureter with a predominance of $\alpha 1_A$ and $\alpha 1_D$ receptor subtypes in the distal one-third of the ureter.[21,22] Alpha-1 adrenergic inhibition reduces the frequency and intensity of peristalsis of the ureter with an increase in the urine flow.[23] Alpha-1 antagonists work on the obstructed ureter by inducing an increase in the intraureteral pressure gradient around the stone, that is an increase in the urine bolus above the stone (and consequently an increase in intraureteral pressure above the stone) as well as decreased peristalsis below the ureter (and consequently a decrease in intraureteral pressure below the stone), in association with the decrease in basal and micturition pressure even at the bladder neck; thereby, an increased chance of stone expulsion. Furthermore, the decreased frequency of phasic peristaltic contractions in the obstructed ureteral tract induced by tamsulosin might determine a decrease in the algogenic stimulus or its absence.[23]

Cervenakov and colleagues in 2002 concluded that

treatment by α1-blockers not only considerably decreased lower urinary tract symptoms, but also helped to accelerate the passage of minor calculi from the terminal part of the ureter in 80.4% of patients. They also suggested that α1-blockers potentiate the spasmo-analgesic action of drugs used in standard treatment.[24] Dellabella and associates in 2003 used tamsulosin as a spasmolytic drug during episodes of ureteral colic due to juxta-vesical calculi. They observed an increased stone expulsion rate with a decrease in stone expulsion time and the need for hospitalization and endoscopic procedures. Particularly, good control of colic pain was provided.[23] Autorino and coworkers[12] administered diclofenac (100 mg/day) in combination with aescin (80mg/day) and Erturhan and colleagues[25] used tolterodine. They did not find a significant difference between two different METs regarding the expulsion time. Corticosteroid drugs seem to induce more rapid stone expulsion in comparison with tamsulosin. In addition, tamsulosin alone as a MET for distal ureteral calculi had excellent expulsive effectiveness.[26]

Tamsulosin that is commonly used in treatment of the bladder outflow obstruction was chosen for the study since it acts selectively on $\alpha 1_A$ and $\alpha 1_D$ receptor subtypes of the ureter, which are able to inhibit basal tone, ureteral contraction, and peristaltic activity and in turn dilating the ureteral lumen and facilitating stone passage with a reduction of the algogenic stimulus.[23] Tamsulosin has been studied as an adjunct therapy with SWL for renal stones and lower ureteral stones. In a randomized non placebo-controlled study enrolling patients with lower ureteral stone undergoing SWL, Kupeli and associates found a significant greater success rate in patients receiving tamsulosin 0.4 mg daily (70.8% versus 33.3.%; $P = .019$) with minimal side effects.[9] Bhagat and colleagues reported an improved success rate with tamsulosin in 60 patients with renal and ureteral stones undergoing SWL (96.6% versus 79.3%; $P = .04$).[10] Conversely, Gravas and coworkers in a cohort study on 64 patients with lower ureteral calculi found a statistically similar success rate in patients receiving or not receiving tamsulosin (66.6% versus 58.1%; $P > .05$).[27] The results of our study suggest that tamsulosin may play a role as an adjuvant to SWL in early clearance of larger ureteral calculi. The frequency of SWL sessions were less in tamsulosin group.

Following SWL, steinstrasse was observed in 2% to 20% of plain x-rays with spontaneous passage in 65%.[28] In a randomized controlled trial with tamsulosin on ureteral steinstrasse, spontaneous clearance occurred in 75% in tamsulosin group and in 65% in placebo group.[14] In another study, Salem and colleagues reported significantly higher stone expulsion rate in tamsulosin group (72.7% versus 56.8%) in patients with steinstrasse.[29] In our study, steinstrasse developed in 8 and 13 patients in tamsulosin and control groups, respectively, and difference was statistically insignificant ($P = .167$). In tamsulosin group, 75% of the patients passed the stone in comparison with 62% in the control group after conservative treatment. Overall 2 patients in tamsulosin group required auxiliary treatment in comparison with 5 patients in the control group and the difference was statistically insignificant ($P = .525$).

One of the most distressing symptoms of ureteral stones is colic. The number of colic episodes and the analgesic requirement have been reported to be significantly lower with the use of tamsulosin. Gravas and associates studied 61 patients with lower ureteral stones undergoing SWL and found that patients receiving tamsulosin required lower dose of analgesic (57 mg versus 119 mg diclofenac equivalent).[28] Autorino and colleagues reported significantly lower analgesic requirement (9% versus 31%) and admission for colic (9% versus 21%) in patients receiving tamsulosin as a MET.[12] In a meta-analysis, Hollingsworth and coworkers reported consistent benefit of tamsulosin in various pain parameters in patients with renal stones as well as ureterolithiasis with or without SWL.[7] Visual analogue scale pain score in our study suggests that number and intensity of pain episodes were significantly less in tamsulosin group.

When the drug was continued beyond 3 months after a single session of SWL, stone clearance continued to occur in the tamsulosin group while in the control group there was only initial improvement.[8] The common side effects of tamsulosin are dizziness, nausea, diarrhea,

headache, and abnormal ejaculation. In our study, the only adverse effect was dizziness in 3 patients and nausea in 5 patients, which was tolerable.

CONCLUSION

Tamsulosin helps in clearance of upper ureteral stones after 1 month of SWL, particularly stones with size of 11 to 15 mm with less requirement of SWL sessions and analgesics.

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CONFLICT OF INTEREST

None declared.

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