

# Tamsulosin as an Expulsive Therapy for Lower Ureteric Calculus after Extra Corporeal Shock Wave Lithotripsy: A Randomized Controlled Study

Santosh Kumar Singh<sup>1\*</sup>, Devendra Singh Pawar<sup>1</sup>, M. S. Griwan<sup>2</sup>

Departments of <sup>1</sup>Urology and <sup>2</sup>Surgery, Pt. B. D. Sharma University of Health Sciences, Rohtak, India

## Abstract

**Background and Aims:** Tamsulosin has been used in several current medical expulsion therapy experiments but the results of studies are variable. Therefore, we conducted a study to evaluate the role of tamsulosin on stone clearance in patients with lower ureteric stone with extracorporeal shock wave lithotripsy (SWL).

**Methods:** A prospective randomized open label study was performed in 119 patients with single lower ureteric calculus undergoing shock wave lithotripsy. The study group received 0.4 mg tamsulosin daily and control group received hydration and analgesic on demand for a maximum of 30 days. Follow up visits were performed at 1, 2, 3 & 4 weeks after ESWL. Efficacy of tamsulosin was evaluated in term of success rate, time for expulsion of fragment & analgesic requirement.

**Results:** The clearance rate was 93% in tamsulosin group and 90% in control group, when stone size was in the range of 4-7 mm and difference was statistically not significant ( $p=0.6$ ). When stone size was in the range of 8-12 mm, the clearance was 80% in tamsulosin group and 52% in control group and difference in statistically significant ( $p=0.021$ ). The mean time to expulsion of the fragments was 12.9 days ( $\pm 7.5$ ) in tamsulosin group and 14.2 days ( $\pm 7.9$ ) in control group and difference was statistically insignificant ( $p=0.561$ ). The mean dose of analgesic used in tamsulosin group was 65.83 mg ( $\pm 48.26$ ) and 116.10 mg ( $\pm 55$ ) in control group. The difference was statistically significant ( $p=0.000$ ).

**Conclusions:** Treatment with tamsulosin appears to be beneficial in lower ureteric stone clearance after ESWL, particularly in larger stone with less need of analgesic.

**Keywords:** Lower Ureteric Calculus, ESWL, Tamsulosin

## Introduction

Symptomatic ureteric calculi represent the most common condition encountered by an urologist in an emergency setting (1). Among all ureteral stones, 70% are found in the lower third of the ureter (2). In the presence of normal renal function and absence of infection, observation is generally preferred for ureteric calculi measuring a maximum of 5 mm (3). However, the spontaneous expulsion rate of distal ureter stone is about 25% if their size is between 4-6 mm, 5% if greater than 6 mm (4) and calculi

over 8 mm are very rarely eliminated spontaneously (5). Therefore, active treatment is recommended for individual with larger stones, especially if their size is greater than 5 mm (6). Extra corporeal shock wave

### \*Correspondence:

Santosh Kumar Singh, MD

Department of Urology,

Pt. B.D. Sharma University of Health Sciences, Rohtak-124001-Haryana, India

Tel: Res. +91-1262-210943,

Offic +91-1262-211301 extn-2670,2225,2721

Fax: +91-1262-21130

E-mail: drsinghsantosh@yahoo.co.in and

drsinghsantoshkumar@gmail.com

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lithotripsy (ESWL) or retrograde endoscopic stone removal comprises the next line of management depending on stone location, size, urgency of clearance, and patient preferences (3).

Recently medical expulsion therapy (MET) has shown promise in facilitating spontaneous clearance of lower ureteric calculi as well as fragments after SWL for renal / or lower ureteric calculi (4, 7-11). Tamsulosin, an  $\alpha 1A$  adrenoreceptor blocker has been used in several current MET experiments but the results of studies are variable (12-14). However it remains unclear whether tamsulosin treatment for patients with distal ureteral stone would improve the stone free rate as the stone size increases.

A prospective randomized study was thus planned to evaluate and compare the effects of tamsulosin with ESWL in lower ureteric calculi of different sizes.

## Materials and Methods

A prospective randomized controlled study was conducted at our institute between January 2006 and June 2008, on out patient department basis. One hundred and twenty consecutive patients older than 18 years of age with symptomatic, unilateral, solitary lower ureteric calculus proved on plain abdominal radiograph, and sonography of kidney- ureter- bladder (KUB) ranging from 4-12 mm in major axis were included in this study. Patients were excluded if they had 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 alpha blockers, calcium channel blockers, steroids, morbid obesity, history of previous failed ESWL. Prior to study complete hemogram, blood urea, serum creatinine, urine complete examination, urine culture sensitivity, X-ray KUB after preparation and sonography of KUB region were carried out on all patients enrolled for the study. The protocol had been approved from our

hospital ethics committee and informed consent was obtained from all patients.

The patients were randomly divided into 2 groups. The patient in group A received 0.4 mg tamsulosin once a day, from the day of ESWL just before the session and continued for one month or the complete clearance of stone, whichever was earlier. The patient in group B did not receive tamsulosin or any other medication known to facilitate expulsion of stone after SWL. The patients of both groups were again divided into two subgroups A1 (stone size 4-7 mm), A2 (stone size 8-12mm) and B1, (stone size 4-7 mm) B2 (stone size 8-12mm) respectively according to size of stone. Single session of ESWL was performed in all patients with electro magnetic Lithotripter (HK –ESWL –VI Shenzhen, China) at 12-15KV. In single session maximum of 3000 shock wave were given. All patients were advised to take 2500 cc fluid daily, antibiotics and analgesic diclofenac on demand during the study period.

The patients were followed up weekly for four weeks. At each follow up, X-ray KUB, Sonography of KUB, urine analysis, blood urea, serum creatinine were performed. Dose of analgesic required, stone free rate, clearance time, and any complications were recorded. Successful results were defined as complete stone clearance or presence of less than 3 mm clinically insignificant, asymptomatic resident calculus. Those who did not complete the follow up without clearance were excluded from study. Unsuccessful patients underwent ureteroscopy as an auxiliary procedure.

## Statistics

Statistical analyses were performed using Student's t test, and Fisher's exact test.  $P < 0.05$  was considered as statistically significant.

## Results

Out of 120 patients, 119 completed the study.

**Table 1.** Demographic and clinical characteristics of both groups

	Tamsulosin group A (n=60)	Placebo group B (n=59)
Mean patient age (years)	34.2 (±13.9)	36 (±12.2)
Sex (male: female)	42:18	42:17
Stone size		
4-7 mm	30	30
8-12 mm	30	29

**Table 2.** Stone clearance stratified by size of stone

Size of stone (mm)	Tamsulosin group A N=60	Placebo group B N=59	P value
4-7	28 (93%)	27 (90%)	0.6
8-12	24 (80%)	15 (52%)	0.021

**Table 3.** Effect of tamsulosin on stone expulsion time and analgesic dose

	Tamsulosin group A	Control group B	P value
Mean expulsion time (days)	12.9 (±7.5)	14.2 (±7.9)	P= 0.56
Mean dose of analgesic (mg)	65.83 (±48.26)	116.10 (±55.00)	P=0.000

One patient from control group was withdrawn from the study due to severe colic and underwent ureteroscopy. Both groups were comparable in their demographic profile (Table1).

The clearance rate was 93% in tamsulosin group and 90% in control group, when stone size was in the range of 4-7 mm and difference was statistically not significant ( $p=0.6$ ). When stone size was in the range of 8-12 mm, the clearance was 80% in tamsulosin group and 52 % in control group and difference was statistically significant, ( $p=0.021$ ) (Table 2).

The mean time for expulsion of the fragments was 12.9 days ( $\pm 7.5$ ) in tamsulosin group and 14.2 days ( $\pm 7.9$ ) in control group and difference was statistically insignificant,  $p=0.561$  (Table 3). The mean dose of analgesic used in tamsulosin group was 65.83 mg ( $\pm 48.26$ ) and 116.10 mg ( $\pm 55.00$ ) in control group. The difference was statistically significant,  $p= 0.000$  (Table 3).

## Discussion

The fragment size is an important factor that

determines the passage of stone through the ureterovesical junction, the narrowest part of the ureter. Spasm, edema or infection may hinder stone passage (15, 16). Ureteric colic, associated with stone, is the manifestation of the visceral pain that is referred to the somatic region corresponding to the spinal segment of the sympathetic supply of the ureter (16). Increased intraluminal pressure due to calculus obstruction and the increased lactic acid production resulting from smooth muscle spasm may have a part in this event (17). Watchful waiting is appropriate for small stone that are not causing acute symptoms and are likely to pass spontaneously (18). Ureteral calculi 4-5 mm in size have a 40-50 % chance of spontaneous passage. In contrast, calculi  $> 6$  mm have a less than 5% chance of spontaneous passage. Majority of the stone that pass do so within a 6 week period after the onset of symptoms (19).

Numerous studies have recently demonstrated promising results in increasing expulsion rate with the addition of drugs for medical expulsion therapy (MET), including corticosteroid, glyceryl trinitrate, prostaglandin synthesis inhibitors, calcium channel

blockers and alpha-adrenoceptor blockers. Treatment with a calcium channel blocker or an alpha-blocker are suggested by recent meta-analysis of nine randomized controlled trials showing that both of these MET 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 in the intramural part of the ureter with a predominance of alpha1A and alpha1D receptor sub types in the distal 1/3 of ureter (20, 21). Alpha1 adrenergic inhibition reduces the frequency and intensity of peristalsis of the ureter with an increase in the flow of urine (22). Alpha1 antagonist 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. Further more, the decreased frequency of phasic peristaltic contractions in the obstructed ureteral tract induced by tamsulosin might determine a decrease in or the absence of the algogenic stimulus (22).

Cervenakov et al (2002) concluded that the treatment by alpha-1 blockers considerably decreased not only lower urinary tract symptoms (LUTS) 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 alpha1 blockers potentiate the spasm-analgesic action of drugs used in standard methods of treatment (23).

Dellabella et al (2003) used tamsulosin as a spasmolytic drug during episodes of ureteric colic due to juxta vesical calculi and observed an increased stone expulsion rate with a decrease in stone expulsion time, and reduced need for hospitalization and endoscopic procedures and provided particularly good

control of colic pain (22). Autorino et al (12) employed diclofenac (100 mg/day) plus aescin (80mg/day) and Erturhan et al (23, 24) used tolterodine, did not find a significant difference between two different MET regarding the expulsion time. Corticosteroid in association with tamsulosin seems to induce more rapid stone expulsion. In addition, tamsulosin alone as medical expulsive therapy for distal ureteral calculi had excellent expulsive effectiveness (25).

Deliveliotis et al (2006) studied the role of alpha1-blockers for treating stent related symptoms. They performed a prospective, randomized, placebo-controlled study to compare the impact of stent symptoms on patients' Quality of life (QOL) using a validated questionnaire (USSQ). Patients who underwent cystoscopically placed stents to treat stone-related hydronephrosis were given 10 mg alfuzosin once daily for 4 weeks. Results showed a decrease in mean urinary symptom index ( $p < 0.001$ ), frequency of stent-related pain ( $p = 0.027$ ), and an improvement in the general health index score ( $p < 0.001$ ) for patients in the alfuzosin group (26).

Tamsulosin also proved to be efficacious in improving stent-related morbidity. In a study by Damiano et al it was shown to decrease flank pain and urinary symptoms at 1 week and increase the general health index score, although this study was not double-blinded or placebo controlled (27).

Tamsulosin, an alpha1 receptor blocker that is commonly used in the treatment of bladder outflow obstruction was chosen for this study as it acts selectively on alpha1A and alpha1D receptor sub types of the ureter which is able to inhibit basal tone, ureteral contraction and peristaltic activity and in turn dilates the ureteral lumen and facilitates stone passage with a reduction of the algogenic stimulus (22). 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 et al (9) found a significant greater success

rate in patients receiving tamsulosin 0.4 mg daily (70.8% vs 33.3%,  $P=0.019$ ) with minimal side effects. Bhagat et al (10) reported an improved success rate with tamsulosin in 60 patients with renal and ureteral stones undergoing ESWL (96.6% vs 79.3%,  $P=0.04$ ). Conversely, Graves et al (7) in a cohort of 64 patients with lower ureteric calculus found a statistically similar success rate in patients with or without tamsulosin (66.6% vs 58.1%,  $P>0.05$ ).

In our study the clearance rate was 93% in tamsulosin group and 90% in control group when stone size were in the range of 4-7 mm and difference was statistically not significant ( $p=0.6$ ). When stone size were in the range of 8-12 mm, the clearance was 80% in tamsulosin group and 52 % in control group and difference was statistically significant ( $p=0.021$ ). The result suggests that tamsulosin may have a role as an adjuvant to ESWL for larger lower ureteric calculi. The mean time for expulsion of the fragments was 12.9 days ( $\pm 7.5$ ) in tamsulosin group and 14.2 days ( $\pm 7.9$ ) in control group and difference was statistically insignificant ( $p=0.56$ ).

In a randomized control trial with tamsulosin on ureteric steinstrass, tamsulosin was not found to be effective in clearance of steinstrass (14). Difference in the reported efficacy of tamsulosin may be related to the type of lithotripter, size, composition and degree of impaction of the calculus.

One of the most distressing symptoms of ureteral stones is colic. The numbers of colic episodes and the analgesic requirement have been reported to be significantly lower with the used of tamsulosin. Gravas et al (4) studied 61 patients with LUS undergoing SWL and found that patients receiving tamsulosin required lower dose of analgesic (57 vs 119 mg diclofenac equivalent). Aurorino et al (12) reported significantly lower incidence of analgesic requirement (9% vs 31%) and admission for colic (9% vs 21%) in patients receiving tamsulosin as MET. In a metanalysis, Hollingsworth et al (7) reported consistent benefit of tamsulosin in various

pain parameters in patient of renal as well as ureterolithiasis with or without SWL.

In our series the mean dose of analgesic used in tamsulosin group was 65.83 mg ( $\pm 48.26$ ) and 116.10 mg ( $\pm 55$ ) in control group. The difference was statistically significant ( $p=0.000$ ).

When the drug was continued beyond three 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 2 patients and nausea in 2 patients which was tolerable. Total duration of study period was 4 week in our study to minimize the side effect of tamsulosin. The majority of the side effect recorded in literature occurred after at least 13 weeks of therapy for benign prostatic hyperplasia (28).

## Conclusion

Treatment with tamsulosin appears to be beneficial in lower ureteric stone clearance after ESWL, particularly in larger stone with less need of analgesic.

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## Conflict of interest:

None declared.

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