



# The Effect of Tamsulosin on Pain and Clearance According to Ureteral Stone Location After Shock Wave Lithotripsy<sup>☆</sup>



Basri Cakiroglu<sup>1</sup>, Orhun Sinanoglu<sup>2,\*</sup>, Mahmure Uraz<sup>3</sup>

<sup>1</sup> Urology Clinic, Hisar Intercontinental Hospital, Umraniye/Istanbul, Turkey

<sup>2</sup> Department of Urology, Maltepe University School of Medicine, Maltepe/Istanbul, Turkey

<sup>3</sup> Department of Emergency Medicine, Maltepe University School of Medicine, Maltepe/Istanbul, Turkey

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## ABSTRACT

**Background:** Medical expulsion therapy has shown encouraging results in facilitating spontaneous clearance of ureteral stones after extracorporeal shock wave lithotripsy. However, no other study has yet determined the benefit of medical expulsion therapy for stones in different ureteral locations.

**Objective:** The aim of the study was to evaluate tamsulosin as adjunctive therapy to extracorporeal shock wave lithotripsy (SWL) in terms of pain clearance of stones in the upper, middle, and lower ureter.

**Methods:** Between June 2008 and July 2011, patients with a solitary ureteral stone that was  $\geq 6$  mm up to 15 mm and located in the upper, middle, or lower ureter undergoing SWL were evaluated. The patients were randomly allocated to a conservative treatment (group 1) and a tamsulosin treatment group (group 2). Administration of the drug was started immediately after SWL and was continued for a maximum of 28 days. Patients were evaluated for stone clearance, time to stone clearance, and number of SWL sessions. The pain intensity was evaluated by visual analog scale.

**Results:** There were 64 patients in the control group and 59 in the tamsulosin group. The average stone sizes were 10.70 (3.20) mm and 11.40 (3.01) mm ( $P = 0.24$ ). Group 1 and group 2 received 2507 (984) and 2759 (775) shock waves ( $P = 0.86$ ), 1.53 (0.8) and 1.49 (0.75) sessions ( $P = 0.85$ ), respectively. Mean visual analog scale scores and times to clearance were 3.81 (2.74) and 2.73 (2.28) ( $P = 0.00$ ) and 12.59 (8.63) days and 8.34 (7.60) days ( $P = 0.00$ ), respectively, for all stones in groups 1 and 2. Only the clearance time of upper ureteral stones between groups showed statistical significance (13.54 [8.32] days vs 7.10 [6.40] days;  $P = 0.00$ ).

**Conclusions:** Tamsulosin may help in the treatment of all ureteral stones after SWL, particularly stones in the upper ureter, with a shorter time to clearance and less need for analgesic drugs.

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## Introduction

Urolithiasis affects 4% to 15% of the world population, and the incidence of this disease is increasing.<sup>1</sup> Ureteral stone disease is one of the important issues that an urologist encounters in emergency clinical settings. Although shock wave lithotripsy (SWL) is accepted in many institutions as the first-line treatment option for patients with ureteral stones, observation can be preferred for ureteric calculi measuring a maximum of 5 mm, in the absence of infection or renal insufficiency.<sup>1</sup> In the stone migration process, ureteral activity is modulated by the sympathetic nervous system.<sup>2</sup> In several studies, the density of  $\alpha_1$ -D-adrenergic receptors in the ureteral smooth muscle cells is greater than that of other adrenergic

receptors.<sup>3</sup> In this context, the  $\alpha_1$ -adrenergic antagonists are able to inhibit basal tone and peristaltic frequency, dilating the ureteral lumen and facilitating stone passage.<sup>4</sup>

These pharmacologic agents, shown to facilitate ureteral stone expulsion and reduce total analgesic drug use, have been used for medical expulsion therapy (MET).<sup>5–7</sup>

Among them, tamsulosin was used in several recent studies, but the results of studies are variable, and most of them were carried out on patients with lower ureteral and renal calculi.<sup>8–10</sup>

To our knowledge, no study has defined the contribution of MET after SWL separately for upper, middle, and lower ureteral stones in terms of pain and clearance time. Thus, we planned to use tamsulosin, as adjunctive therapy, to evaluate its role in treating stones in different ureteral locations.

## Materials and Methods

Between June 2008 and July 2011, patients with a solitary ureteral stone that was  $\geq 6$  mm up to 15 mm and located in the

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\* Address correspondence to: Orhun Sinanoglu, OS, Maltepe Üniversitesi Tıp Fakültesi Üroloji Anabilim Dalı, Feyzullah Caddesi, No. 39, PK:34843, Maltepe/Istanbul, Turkey

E-mail address: [orhundr@hotmail.com](mailto:orhundr@hotmail.com) (O. Sinanoglu).

upper, middle, or lower ureter underwent SWL at our institution. Written informed consent was obtained from each participant, and the institutional review board approved our study. The assessment of stone size and location was performed by plain x-ray of the kidneys, ureters, and bladder (KUB) and/or ultrasound imaging. The exclusion criteria were age younger < 18 years; weight < 50 kg or > 100 kg; severe skeletal malformation; pregnancy; aortic and/or renal artery aneurysm; a history of drug or alcohol abuse; long-term use of drugs such as antidepressants, histamine blockers, and anxiolytics and allergy to one of the study medications; concomitant treatment with calcium antagonists and/or an  $\alpha_1$ -adrenergic antagonist; concomitant renal stones; previous unsuccessful attempts at SWL; elevated serum creatinine (> 2 mg/dL); urinary tract infection; diabetes; peptic ulcers; history of spontaneous stone expulsion; hypotension; coagulopathy; urinary congenital anomalies; or previous nephroureteral surgery. The patients were randomly allocated to conservative treatment (group 1) and tamsulosin treatment (group 2) using the coin toss method in order to choose the nontreatment and Tamsulosin arms. All patients were evaluated before treatment with KUB and renal ultrasonography. Before lithotripsy, clinical (history and brief physical examination) and laboratory (complete blood count, urine culture, renal function, coagulation parameters screening, and pregnancy test) examinations were conducted. Additional KUB and ultrasonography were performed just before lithotripsy. Drug administration was started immediately after SWL and was continued for a maximum of 28 days or until an alternative treatment was started. The patients who were not stone free at this examination were excluded from the study and underwent additional treatment. A total of 123 patients met these requirements. Group 1 (64 patients) received standard medical therapy alone and was used as the control group. Group 2 (59 patients) was assigned to receive our standard medical therapy in association with 0.4 mg tamsulosin once daily. Our standard medical therapy after SWL was 75 mg diclofenac injected intramuscularly on demand. A gastroprotective therapy (40 mg pantoprazol once daily) was given to every patient. After discharge, all patients were instructed to drink a minimum of 2 L of water daily and were asked to complete a diary about post-discharge pain, stone expulsion, use of analgesic drugs, and side effects of medical therapy. Patients were evaluated for stone clearance, time to stone clearance, and number of SWL sessions. The pain intensity was evaluated with the visual analog scale (VAS). The patients were requested to define pain in a scale of 1 to 10 by comparing it with the most severe pain the patients could imagine (0, no pain, to 10, the most severe pain imagined). Follow-up included clinical examination, urinalysis with culture and sensitivity testing as required, renal KUB, and/or ultrasonography, repeated 5 days after each lithotripsy session.

The final examination was performed with ultrasonography or helical computed tomography at day 28 to confirm stone-free status. All SWL treatments were performed with Storz Medical AG Modulith Slk (Tägerwilen, Switzerland) with both ultrasonic and fluoroscopic focusing. The mean intensity and number of shock waves after the first SWL session were 18.5 kV (range, 6–19) and 3140 (range, 2700–3600). Statistical analysis was performed using SPSS software, version 16.0 (SPSS Inc, Chicago, Illinois). The differences between groups 1 and 2 were tested using the *t* test, Mann-Whitney *U* test,  $\chi^2$  test, and Fisher exact test. *P* < 0.05 was considered statistically significant.

**Results**

Demographic and clinical characteristics of all patients are summarized in **Table I**. The data for the 123 patients who completed follow-up without dropping out met the criteria; 64

**Table I**  
Demographic and clinical characteristics of all patients with ureteral stones stratified into groups.\*

Variable	Group 1 (N = 64)	Group 2 (N = 59)	P
<b>Demographic</b>			
Sex distribution, male:female	51:13	47:12	0.99
Age, y	42.19 (13.17)	44.66 (13.25)	0.32
Stone size, mm	10.70 (3.20)	11.40 (3.01)	0.24
<b>Clinical</b>			
No. of SWL sessions	1.53 (0.8)	1.49 (0.75)	0.85
Mean shock waves/session	2507 (984)	2759 (775)	0.86
Pain, VAS score	3.81 (2.74)	2.73 (2.28)	0.00
No. of days to clearance	12.59 (8.63)	8.34 (7.60)	0.00

SWL, shock wave lithotripsy; VAS, visual analog scale.

\* Continuous variables are presented in mean (SD).

in group 1 and 59 in group 2. The average stone sizes were 10.70 (3.20) mm and 11.40 (3.01) mm (*P* = 0.24). The patients in the 2 groups underwent SWL treatment. Groups 1 and 2 received 2507 (984) and 2759 (775) shock waves (*P* = 0.86) and underwent 1.53 (0.8) and 1.49 (0.75) sessions (*P* = 0.85), respectively. Statistically significant differences in terms of pain score (3.81 [2.74] vs 2.73 [2.28], *P* = 0.00) (**Table II**) and clearance time (12.59 [8.63] days vs 8.34 [7.60] days, *P* = 0.00) (**Table III**) for all stones were found between groups 1 and 2. The difference in VAS score between the groups was not statistically significant if the stones were classified according to upper, middle, and lower ureteral locations (**Table II**). Only the clearance time of upper ureteral stones between groups showed statistical significance (13.54 [8.32] vs 7.10 [6.40], *P* = 0.00) (**Table III**). The mean cumulative diclofenac dose was 375 mg (5 injections) per patient in group 1 and 225 mg (3 injections) per patient in group 2, with a statistically significant difference between the 2 groups (*P* = 0.00). No relevant side effects in connection with tamsulosin that would cause the medication to discontinued were observed during follow-up.

**Discussion**

The first-line treatment options for patients with upper ureteral calculi with < 1.5 cm in size are extracorporeal SWL and flexible ureterorenoscopic lithotripsy.<sup>1</sup> Fragment expulsion after renal SWL is similar to spontaneous discharge of the stone itself. The narrowest part of the ureter is the ureterovesical junction, and spasm, edema, or infection of this location may impede stone passage.<sup>1,6</sup> The pain associated with the obstructing stone is called renal or ureteral colic and is a visceral pain that refers to the somatic region corresponding to the spinal segment of the sympathetic efferent of the ureter.<sup>11</sup> Many studies suggest that edema, infection, spasm, and ureteral peristalsis may be improved by an appropriate medical therapy. Furthermore,  $\alpha_1$ -adrenergic antagonists may decrease ureteral peristaltic frequency, reducing spasm in ureteral smooth muscle, and an increase in the rate of fluid transport follows these changes.<sup>4,6</sup>

**Table II**  
Comparison of mean (SD) pain scores according to ureteral stone location.

Stone Location	Group 1 (N = 64)	Group 2 (N = 59)	P
Upper ureter (n = 57)	4.00 (2.58) (n = 28)	2.90 (2.19) (n = 29)	0.69
Middle ureter (n = 28)	3.00 (3.91) (n = 12)	2.38 (2.42) (n = 16)	0.56
Lower ureter (n = 38)	4.00 (2.71) (n = 24)	2.79 (2.42) (n = 14)	0.12

VAS, visual analog scale.

**Table III**  
Comparison of stone clearance times according to ureteral location.

Stone Location	No. (SD) Days to Clearance		P
	Group 1 (N = 64)	Group 2 (N = 59)	
Upper ureter (n = 57)	13.54 (8.32) (n = 28)	7.10 (6.40) (n = 29)	0.00
Middle ureter (n = 28)	10.75 (8.20) (n = 12)	9.25 (9.95) (n = 16)	0.56
Lower ureter (n = 38)	12.42 (9.38) (n = 24)	9.86 (6.94) (n = 14)	0.42

In this study, tamsulosin was chosen from among the available  $\alpha$ -blockers because it is a combined  $\alpha_{1A}$  and  $\alpha_{1D}$  selective adrenergic antagonist, considering studies that demonstrated the existence of  $\alpha_{1A}$  and  $\alpha_{1D}$  adrenoceptor subtypes in the smooth muscle cells of the human ureter.<sup>4</sup> Tamsulosin increases the urine bolus and intraureteral pressure above the stone. It also decreases peristalsis below the ureter, which consequently lowers intraureteral pressure in association with the decrease in basal and micturition pressure, even at the bladder neck; thus, it increases the chance of stone expulsion. Furthermore, the phasic peristaltic contractions also decrease in the obstructed ureter, which leads to an eventual decrease in the painful stimulus.<sup>6</sup> Several studies in the past decade investigated the issue.

In a randomized, nonplacebo-controlled study enrolling patients with lower ureteral stones undergoing SWL, a significantly greater success rate was obtained in patients receiving tamsulosin 0.4 mg/d (70.8% vs 33.3%;  $P < 0.019$ ) with minimal side effects.<sup>12</sup>

Another study reported an improved success rate with tamsulosin in 60 patients with renal and ureteral stones undergoing SWL (96.6% vs 79.3%;  $P < 0.04$ ).<sup>9</sup> In contrast to these reports, a study with 64 patients receiving SWL for lower ureteral stones found a statistically similar success rate in patients with or without tamsulosin (66.6% vs 58.1%;  $P > 0.05$ ).<sup>13</sup>

It is also worth noting that among the drugs used for MET, only corticosteroids seem to induce more rapid stone expulsion compared with tamsulosin.<sup>14</sup>

With regard to the present study, we found a favorable effect of tamsulosin in clearance time of fragments after SWL, regardless of ureteral position of the initial stone. When the stones were classified according to ureteral location, the clearance time for only upper ureteral stone fragments was significantly shorter compared with the control group.

Besides decreasing clearance time, investigators also suggest that  $\alpha_1$ -blockers potentiate the spasmolytic action of drugs used in standard treatment.<sup>15</sup>

The use of tamsulosin as a spasmolytic drug during episodes of ureteral colic due to calculi in the ureterovesical junction also seems beneficial. Several authors reported an increased stone expulsion rate with a decrease in stone clearance time and the need for hospitalization particularly, with good control of pain.<sup>6</sup> The number of colic episodes and the needs for analgesic drugs seems to be significantly lower with the use of tamsulosin.<sup>13</sup> In 2 recent studies evaluating clearance time and decrease in pain for only upper ureteral stones, the authors reported unanimously that passage of fragments was faster, although a significant advantage in terms of decreasing pain associated with tamsulosin was not certain in 1 of these 2 series.<sup>16,17</sup>

In parallel with the previously mentioned reports, VAS scores in our patients using tamsulosin after SWL were significantly lower compared with the control group, regardless of stone location, although the difference between groups was not statistically significant when the stones were classified according to ureteral location. However, to ensure such significance, the number of groups for each ureteral location was limited in our

series. Last, the adverse effects of tamsulosin were dizziness in 2 patients and nausea in 6 patients, which was tolerable and required no additional treatment.

## Conclusions

Tamsulosin helps in the treatment of stones after SWL, particularly stones in the upper ureter, with a shorter clearance time and less need for analgesic drugs. Larger comprehensive series for stones in different ureteral locations may demonstrate significant benefits of tamsulosin after SWL.

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Mr. Cakiroglu conceived the idea, helped in data collection, and drafted part of the manuscript. Mr. Sinanoglu analyzed the data, performed the literature search, and wrote most of the manuscript. Mrs. Uraz helped in patient selection and data collection.

## Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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