

## Effects and outcome of Tamsulosin more than just stone clearance after extracorporeal shock wave lithotripsy for renal calculi

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### Abstract

**Objective:** To determine the effect of Tamsulosin, as adjunctive medical therapy after Extracorporeal Shock Wave Lithotripsy for renal stones on rate of stone clearance, clearance time, pain intensity during stone clearance, steinstrasse formation and auxiliary surgical intervention required.

**Method:** A prospective randomized controlled study was carried out in 120 patients who underwent ESWL for renal stones of 0.5-2.0cm. They were randomized into study and control group in which Tamsulosin 0.4mg/day was given in former as an adjunctive medical therapy. All patients underwent ESWL every 2 weeks until complete stone clearance for 8 weeks. The parameters assessed were stone clearance, clearance time, pain intensity and effect on steinstrasse.

**Results:** Of the 120 patients 60 were in each group. The stone clearance rate was greater in study than in control group, 58(96.7%) vs. 48(80%) respectively, ( $p<0.004$ ). The mean stone clearance time was observed earlier in study group as compared to control group with significant statistical difference in stone size between 0.6-1.5cm. The mean intensity of pain patients experienced according to Visual analogue scale (VAS) was significantly less in study group ( $p<0.002$ ). The rate of steinstrasse formation was observed to be higher in control than in study group 15(25%) vs 6(10%) respectively ( $p<0.003$ ), while its spontaneous clearance was higher in study group than in control group 83.3% vs 33.3% ( $p<0.03$ ).

**Conclusion:** Tamsulosin significantly increases stone clearance after shock wave lithotripsy for renal stones. It also appeared to facilitate earlier stone clearance, reduces severity of pain, reduces the incidence of steinstrasse formation and tends to facilitate its spontaneous clearance.

**Keywords:** Extracorporeal Shockwave Lithotripsy, Tamsulosin, Medical expulsive Therapy, Steinstrasse, Renal stone. (JPMA 64: 644; 2014)

### Introduction

Extracorporeal Shock Wave Lithotripsy (ESWL) is the main modality of treatment in renal stones  $\leq 2.0$ cm in size.<sup>1</sup> Recently many agents such as calcium channel blockers, corticosteroids, non-steroidal anti-inflammatory drugs and alpha blockers have been used to facilitate stone passage along the ureter. The role of alpha blockers is known to facilitate ureteral stone clearance due to presence of alpha adrenergic receptors along the ureter.<sup>2-4</sup>

The role of alpha blockers as an adjunctive to ESWL for renal stones has emerged and is generally accepted for the last few years. However there is paucity of studies that have delved into the role of alpha blockers beyond just stone clearance.<sup>5-7</sup>

So the aim in this study was to elucidate the broader role of alpha blocker not only in rate of stone clearance but its effect on clearance time, pain, steinstrasse and auxiliary

procedure required, after ESWL for renal calculi.

### Patients and Methods

This randomized non placebo-controlled study was conducted at The Kidney Centre (Post Graduate Training Institute) Karachi, from July to December 2010. Informed consent was taken from all the patients. Patients with single radio-opaque renal stone (0.5-2.0cm) were enrolled. The exclusion criteria included age extremes (18-60 years), recent open or endoscopic surgical intervention, presence of ureteral stent, radiolucent calculus, past unsuccessful ESWL, renal impairment (Serum Creatinine level above normal range), urinary tract infection, those on calcium channel blocker or alpha adrenergic antagonist and corticosteroids, congenital urinary anomalies, severe vertebral malformation.

A total of 120 patients matched all the selection criteria and were included in the study. All the patients were already evaluated in Out Patient Department (OPD) with history, clinical examination and investigations; that included: Complete Blood Count, serum creatinine, urine culture and radiological investigations (ultrasound KUB,

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Intravenous Urography or CT-pyelogram). After ESWL, they were randomly assigned by envelop method to either standard therapy or alpha blocker (Tamsulosin) administration. The drug administration was started immediately after the ESWL and was continued for a maximum of 2 months or until an alternative treatment was applied. Study group (n=60) was assigned to receive Capsule Tamsulosin 0.4mg once daily whereas control group (n=60) did not receive Tamsulosin following ESWL.

Both the groups were given intravenous analgesia (Pethidine according to body weight) along with intravenous antiemetic Metoclopramide 10mg prior to each ESWL session and were prescribed oral Diclofenac sodium 50mg BD for 1 day only. After the session of ESWL, patients of both the groups were explained and provided Visual analogue scale (VAS) (0 - no pain / 1-4: mild / 5-6: moderate / 7-10: severe), so that they could mark the intensity of pain on VAS whenever it occurred and bring it along in the follow-up OPD. Patients of both the groups were followed in OPD weekly with x-ray KUB and VAS if they had experienced any pain during the previous week. The need for more sessions of ESWL was decided after assessing the findings in the X-ray KUB. The subsequent sessions of ESWL needed were given after every 2 weeks.

In case of severe pain, patients were advised to approach our emergency department, get assessed by our medical officer and if need be given parental analgesia for immediate relieve of pain and in case of persistent pain, fever or haematuria would be managed accordingly and admitted if need be. Final outcome was measured once 8 weeks of treatment was completed.

ESWL was given using available Storz Medical Modulith SLK, electromagnetic shock wave generator. Maximum of 4000 shocks at rate of 120/min and to maximum of 70KV per session was given by our skilled and designated Medical officer with experience of 10 years, in lithotripsy department. Factors analyzed were stone clearance rate, time to stone clearance (in weeks), mean intensity of pain (mild, moderate and severe), incidence of steinstrasse formation and incidence of auxiliary procedure required.

### Statistical Analysis

On assuming  $P_1 = 96.6\%$ ,  $P_2 = 79.3\%$  (where  $P_1$  and  $P_2$  are the proportion in population taken from related reference study<sup>7</sup>), alpha (default) =  $5\%(0.05)$ ,<sup>8,9</sup> Power  $1-\beta$  (default) =  $80\%$  (0.8),<sup>10</sup> sample size of 55 in each group was determined using web based Power/sample size calculator.<sup>11</sup> Considering probability of drop out cases in the study, 60 patients in each group were included. The categorical demographic and outcome variables were compared using the chi-square test or Fisher's exact test.

The parametric demographic and outcome variables were compared using an independent sample t test. All the pre-assumptions for all statistical tests used were checked and their use was justified. All p values less than 0.05 were considered statistically significant. All the required information was recorded in a specially designed Performa. SPSS 13.00 was used to analyze the collected data.

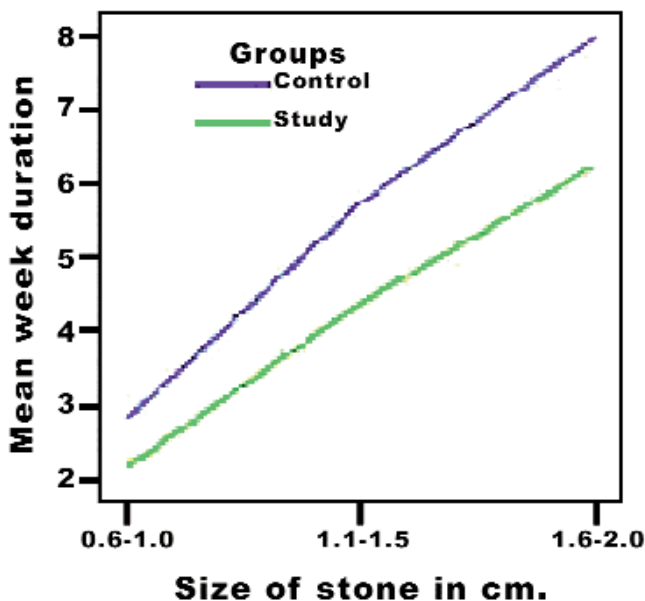
### Results

Of the 120 patients 60 were in control group and 60 were in study group. None of the 120 patients included in the study dropped out and all were followed till the end of the study. The 2 groups were comparable in their baseline demographic and clinical characteristics (Table-1). Mean age of patients in control and study group were  $41\pm 13.1$  years and  $39\pm 14.7$  years respectively ( $p < 0.26$ ). Mean size of the stone in control and study group was  $1.05\pm 0.26$  cm and  $1.12\pm 0.31$  cm respectively ( $p < 0.19$ ). Different ranges of size of stone was also assessed separately and were found comparable between both groups ( $p < 0.13$ ). Similarly, there was no statistically significant difference between the 2 groups with regards to side, site and size of stone, their gender and age.

The overall stone clearance rate in control and study group was 48 (80%) and 58 (96.7%), the difference was statistically significant ( $p < 0.004$ ), (Table-2). The size of the stone was stratified into 3 groups 0.6-1.0, 1.1-1.5 and 1.6-2.0cm and accordingly stone clearance were analyzed. The stone clearance of 0.6-1.0cm stone size in control and study group was 39/41 (95.1%) and 31/31 (100%) respectively which was statistically insignificant ( $p < 0.21$ ). In the 1.1-1.5 stone size group, clearance was 8/14 (57.1%) and 23/24 (95.8%) in control and study group

**Table-1:** Demographic characteristics of the patients.

	Control (%)	Study (%)	P-value
No.	60	60	0.45
Gender: Male	48 (80)	41 (68.3)	0.14
Female	12 (20)	19 (31.7)	0.26
Mean age	41( $\pm 13.1$ )	39( $\pm 14.7$ )	
Side: Left	31 (51.7)	29 (48.3)	0.71
Right	29 (48.3)	31 (51.7)	
Site: Pelvis	43 (71.7)	36 (60)	0.57
Lower	13 (21.7)	17 (28.3)	
Mid	3 (5.0)	5 (8.3)	
Upper	1 (1.7)	2 (3.3)	
Mean size cm	1.05 ( $\pm 0.26$ )	1.12 ( $\pm 0.31$ )	
(range cm)	(0.6-1.9)	(0.6-1.9)	0.19
0.6-1.0cm (%)	41 (68.3)	31 (51.7)	0.13
1.1-1.5cm	14 (23.3)	24 (40)	
01.6-2.0cm	5 (8.3)	5 (8.3)	



**Figure:** Line chart demonstrating mean week duration for stone clearance in both the groups.

**Table-2:** Comparison of all the endpoints between the two groups.

	Control (%)	Study (%)	P-value
Overall Stone clearance	48 (80)	58 (96.7)	0.004
Stone clearance acc. to size:			
0.6-1.0cm	39/41 (95.1)	31/31 (100)	0.21
1.1-1.5cm	8/14 (57.1)	23/24 (95.8)	0.003
1.6-2.0cm	1/5 (20)	4/5 (80)	0.05
Pain Intensity:			
No pain (0)	0	1 (1.7)	0.002
Mild pain (1-4)	37 (61.7)	50 (83.3)	
Moderate pain (5-6)	8 (13.3)	8 (13.3)	
Severe pain (7-10)	15 (25)	1 (1.7)	
Steinstrasse:			
Steinstrasse	15 (25)	6 (10)	0.03
With Stone clearance	5/15 (33.3)	5/6 (83.3)	0.03
Surgical Intervention	10 (16.7)	1 (1.7)	0.004

respectively, statistically significant ( $p < 0.003$ ). In the 1.6-2.0cm stone size group, clearance was 1/5 (20%) and 4/5 (80%) in control and study group respectively, statistically significant ( $p < 0.05$ ) (Table-2). So larger stones between 1.1cm to 2.0cm showed better stone clearance in study as compared to control group with statistically significant difference.

The mean stone clearance time for 0.6-1.0cm stone was  $2.16 \pm 0.96$  weeks (1-3 range) and  $2.82 \pm 1.16$  weeks (1-5 range) for study and control group respectively ( $p < 0.0001$ ). Similarly for 1.1-1.5cm stones mean stone

clearance time was  $4.39 \pm 0.98$  weeks (3-6 range) and  $5.75 \pm 1.16$  weeks (4-7 range) for study and control group respectively ( $p < 0.002$ ) and for 1.6-2.0cm stones, mean  $6.25 \pm 0.95$  weeks and 8 weeks respectively, with range 5-7 weeks in study group and only 1 had successful stone clearance at 8 weeks in control group ( $p < 0.172$ ). So in all 3 ranges of stone sizes from 0.5 to 2.0 cm it was observed that the stone clearance was earlier in study group as compared to control group with significant statistical difference in stone size between 0.6-1.5cm. Graphically mean stone clearance time in weeks is shown in Figure.

The mean intensity of pain patients experienced according to Visual analogue scale (VAS) was assessed by the end of 8 weeks. Most of the patients in the study group had either no pain or mild pain 51(85%), moderate pain 8(13.3%) and only 1(1.7%) had severe pain whereas in control group, 37(61.7%) had mild pain, 8(13.3%) had moderate pain and 15(25%) had severe pain, the difference was statistically significant ( $p < 0.002$ ) (Table-2).

Steinstrasse was observed in 15(25%) and 6(10%) in control and study group respectively with significant statistical difference ( $p < 0.03$ ). Five out of 6 (83.3%) patients had spontaneous stone clearance in the study group whereas only 5 out of 15 (33.3%) patients had spontaneous stone clearance in control group with significant statistical difference ( $p < 0.03$ ) (Table-2).

Only 1(1.7%) patient in study group underwent ureteroscopy (URS) for steinstrasse whereas 10(16.7%) patients in control group needed intervention URS, showing a statistically significant difference ( $p < 0.004$ ).

### Discussion

The primary goal of renal stone management is to achieve maximum stone clearance with minimum morbidity to the patient. The introduction of ESWL and continuing advancements in the field of endourology have allowed most patients with renal stones to be treated in a minimally invasive fashion.

ESWL has revolutionized the non-invasive treatment of renal and ureteral calculi. ESWL has become the main modality for treatment of renal stones  $\leq 2.0$ cm. For renal stones, the clearance may be influenced by fragmentation, calyceal anatomy and ureteral clearance. After the passage of the stone in the ureter, the clearance rate is dependent on ureteral factors such as oedema and ureteral spasm as well as fragment size.<sup>12-14</sup>

Ureteral relaxation in the region of the stone is considered to be an important factor promoting stone passage. Recently there has been renewed interest in medical

expulsive therapy, which targets some of the reversible factors for stone passage in the ureter.<sup>2-4</sup>

There is evidence of prevalence of alpha 1 AR subtypes ( $\alpha$ 1A,  $\alpha$ 1B and  $\alpha$ 1D) in the human ureter, with  $\alpha$ 1D and  $\alpha$ 1A more prevalent over  $\alpha$ 1B ARs.<sup>15-18</sup>

Thus, the rationale of using alpha 1 adrenergic antagonists in medical expulsion therapy lies in their capability to inhibit basal tone and peristaltic ureteral contractions, dilating the ureteral lumen and thereby increasing the fluid bolus volume facilitating stone passage down the ureter.<sup>2-4</sup> It also acts on the C fibers blocking pain conduction.<sup>19</sup> Of the available  $\alpha$ 1-blockers, Tamsulosin is chosen for this study as it is a combined  $\alpha$ 1A and  $\alpha$ 1D-selective adrenergic antagonist.

The aim of this study was to evaluate the use of the alpha antagonist tamsulosin as an adjuvant therapy after ESWL for renal stones to evaluate the clearance rate, clearance time, pain intensity, incidence of steinstrasse formation and its clearance and the incidence of need of auxiliary procedure for the clearance of steinstrasse.

In a study by Bhagat et al.<sup>7</sup> on 60 patients who had mixed ureteral and renal single stone and were randomized to placebo versus tamsulosin after ESWL, the overall success stone clearance rate was significantly better in the study group compared with the control group (96.6% vs 79.3% $p=0.04$ ). With larger stones 11 to 24 mm the difference in the clearance rate was significant ( $p<0.03$ ) but not so with the smaller stones 6 to 10mm ( $p<0.35$ ). Similarly, Gravina et al.<sup>5</sup> reported, of the 130 patients, 78.5% of those receiving tamsulosin and 60% of controls had achieved clinical success at 3 months ( $p<0.037$ ). When they stratified patients according to stone size, for those with a stone size larger than 10mm, the success rate was significantly greater in the tamsulosin group ( $p<0.028$ ).

We had similar results regarding the overall stone clearance which was higher in the study group than in control group (96.7% vs 80%) ( $p<0.004$ ). In particular, larger stones above 1.1cm to 2.0cm showed significantly better stone clearance in study as compared to control group. In the 1.1-1.5cm stone size group, clearance was 8/14 (57.1%) and 23/24 (95.8%) in control and study group respectively, ( $p<0.003$ ). In the 1.6-2.0cm stone size group, clearance was 1/5 (20%) and 4/5 (80%) in control and study group respectively, ( $p<0.05$ ).

Naja et al.<sup>6</sup> reported that tamsulosin helped reduce the number of days required for clearance especially for stones <1.0cm. In this study, the stone clearance was earlier in the study group as compared to the control group in all 3

ranges of stone sizes from 0.6 to 2.0cm, but difference was statistically significant in group of stone range of 0.6-1.5cm. This is similar to the results of Najact et al.<sup>6</sup>

The main problem suffered by patients after undergoing ESWL is the pain associated with the passage of fragments along the ureter. Gravina et al.<sup>5</sup> reported a lower incidence of colic (26.1% vs 76.9%,  $p<0.001$ ) and a lower need of diclofenac ( $p<0.001$ ) in the tamsulosin group. Bhagat et al.<sup>7</sup> reported a lower dose of analgesics for the tamsulosin group, but this was not statistically significant. Naja et al.<sup>6</sup> also reported a similar results regarding the lower incidence of pain on a visual analogue scale score ( $28.67\pm 0.35$  vs  $47.30\pm 24.98$ ,  $p<0.0001$ ) in tamsulosin group.

Similarly, in this study the intensity of pain was assessed using VAS and the mean was analyzed at the end of 8 weeks. So overall the mean intensity of pain experienced in study group was lesser than the control group ( $p<0.002$ ) which was statistically significant.

In Bhagat et al's study,<sup>7</sup> of the 18 patients who developed steinstrasse, 10 were in the study group and 8 in the placebo group. All 10(100%) in the study group cleared spontaneously compared to 6 (75%) in the placebo group. Naja et al.,<sup>6</sup> reported that 3.9% in the study group and 13.8% in control group developed steinstrasse ( $p<0.1$ ) although insignificant but greater rate of spontaneous clearance was observed in the study group.

In this study, the incidence of steinstrasse was higher in the control than in study group 15(25%) vs 6(10%) respectively, ( $p<0.03$ ) Spontaneous stone clearance was higher in the study group (83.3%) which compares well with results of the study by Bhagat et al.<sup>7</sup>

Tamsulosin is well recognized and established drug with known usage and side effects. A few Randomized control trials (RCT) have been reported using the same drug to acquire similar objectives.<sup>5-7</sup>

## Conclusion

Tamsulosin not only significantly increases rate of stone clearance after shock wave lithotripsy for renal stones but also facilitates earlier stone clearance, reduces severity of pain, and incidence of steinstrasse formation and tends to facilitate its spontaneous clearance.

These advantages could translate into lower treatment costs and complications, an early return to work and better patient acceptance of the treatment. Nevertheless, the role of tamsulosin in adjunction with ESWL needs to be assessed more with a larger scale confirmative trial before final clinical recommendations can be made.

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