

## EFFICACY OF SELECTIVE ALPHA-1 RECEPTOR BLOCKERS (TAMSULOSIN) IN FACILITATING THE PASSAGE OF RENAL STONES AFTER EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

Nauman Khalid <sup>a</sup>, Aijaz Hussain Memon <sup>b</sup>, Wasim Sarwar Bhatti <sup>c</sup>, Hanan Noor <sup>d</sup>, Muhammad Waqas Iqbal <sup>e</sup>, Muhammad Sohail<sup>g</sup>, Asad Ramzan<sup>f</sup>

<sup>a</sup> Assistant Professor Department of Urology, Madinah Teaching Hospital, Faisalabad.

<sup>b</sup> Assistant Professor, Department of Urology and Nephrology, Peoples University of Medical and Health Sciences for Women Nawabshah.

<sup>c</sup> Assistant Professor, Department of Urology/ Nephrology and Renal Transplantation, Gambat Institute of Medical Sciences/ Gambat Medical College, GIMS Gambat.

<sup>d</sup> Senior Registrar, Department of Urology, Kidney Centre District Headquarter Hospital Faisalabad.

<sup>e</sup> Senior Registrar, Department of Urology, Madinah Teaching Hospital, Faisalabad.

<sup>f</sup> Student Shalamar Medical College Lahore.

### ABSTRACT:

**BACKGROUND & OBJECTIVE:** Urinary system stone disease is a common entity. Small renal stones are preferably treated using Extracorporeal Shock Wave Lithotripsy (ESWL) technique. Passage of stone fragments result in pain, hematuria and urinary tract obstruction. This can be avoided by the use selective  $\alpha$ -1 receptor antagonists like Tamsulosin. However, their efficacy remains a matter of debate. In this study the role of selective  $\alpha$ -1 blocker was evaluated in facilitating spontaneous expulsion of renal stone fragments after ESWL. The objective of our study was to find out the Efficacy of Tamsulosin (Selective  $\alpha$ -1 blocker) in facilitating the transit of stone fragments (4-7mm) after ESWL. Follow up X-ray KUB was used to confirm the stone clearance. Efficacy was measured in terms of stone expulsion rate.

**METHODOLOGY:** It was randomized controlled trial including 150 patients coming to outpatient department of Urology Lahore General Hospital, Lahore from January 25, 2010 to July 25, 2010. Total 150 patients with renal stones broken down into fragments (4-7mm) after ESWL were enrolled using non-probability purposive sampling technique. Patients were categorized into group A and B. Patients of group A received cap. Tamsulosin 0.4mg along with Tab. Diclofenac sodium 50mg. Whereas, patients belonging to group B received only diclofenac sodium 50 mg twice daily. Patients underwent ESWL every three weeks, in case of non-fragmentation, to the maximum of 4 sessions. All the patients were followed with X Ray KUB for stone clearance. The data of all patients was incorporated into pre designed Performa. Statistical evaluation of clinical variables done in terms of efficacy i.e. stone clearance.

**RESULTS:** Stone clearance rate of patients in group A was 86.6% as compared to only 76% in group B. Usage of selective  $\alpha$ -1 blockers in group A enhanced the stone clearance rate as compared to group B. However this difference was statistically insignificant (p-value-0.094).

**CONCLUSION:** There was increased stone clearance in alpha one blocker group but not statistically significant. Further studies with larger sample size are required to evaluate the role of Selective  $\alpha$ -1 blockers (Tamsulosin) after ESWL.

**KEYWORDS:** Alpha blocker, Renal stone fragments, ESWL, Tamsulosin.

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**INTRODUCTION:**

The urinary system stone disease has 12% prevalence globally <sup>[1]</sup>. Urolithiasis also comprises of 40-50% of urological patients coming to urologist <sup>[2]</sup>. Urolithiasis has recurrence rate of 75% at 20 years after the 1<sup>st</sup> diagnosis. 20% patients suffering from urolithiasis are diagnosed to have ureteric stone. Amongst these, 70% reside in the lower ureter <sup>[1]</sup>. Use of selective  $\alpha$ -1 blockers in lower ureteric stones has been advocated by many researchers. Apart from easy administration of these  $\alpha$ -1 blockers, they are also well tolerated. Renal stones broken down after ESWL into fragments that can pass into ureter (4- 7mm) also behave as ureteric calculi. ESWL was introduced in 1980. Before this time, open surgery was the mainstay of treatment for those stones which are unable to pass through the urinary tract. However, ESWL has now become the preferred choice for the small sized renal stones. Compared with open or endoscopic procedures, ESWL is least invasive and achieves almost equal stone clearance in appropriate patients. Renal stones are fragmented by the use of ESWL which are later expelled from the collecting system spontaneously. Stones broken down into fragments after extra corporeal shockwave lithotripsy have to pass through ureter, before it can be passed onto bladder. The management of ureteral stone fragments after ESWL for renal calculi is not different from that of ureteral stones. Renal stone fragments and calculi form in kidney. Due to gravitational force and peristalsis, these fragments pass through the ureter spontaneously <sup>[3]</sup>. Distal ureteric stones may cause severe colicky pain. Over the last 20 years, significant advances have been made in

*Corresponding Author:*

Dr. Nauman Khalid  
Assistant Professor Department of Urology,  
Madinah Teaching Hospital, Faisalabad.  
Email: [drnaumankhalid@hotmail.com](mailto:drnaumankhalid@hotmail.com)

the management of urolithiasis. With advent of ESWL, small caliber flexible endoscopes, development of the intracorporeal lithotripters which allow access to entire urinary tract with little or no compromise of renal functions. As a consequence, open surgery is rare to be first treatment option. However surgical procedures have their risks and they are expensive. Numerous case series have described rates of spontaneous passage based on stone size and location. We have found that 95% of ureteral stones 2 to 4 mm in size will pass spontaneously. This drops to 50% for stones greater than 5 mm. Stones greater than 6 mm have a lower rate of spontaneous passage. Duration of stone passage may be as long as 40 days <sup>[4]</sup>. Hence conservative management is proposed for these patients <sup>[5]</sup>. Spontaneous ureteric stone expulsion depends upon a number of factors. These factors are either related to the stone or with the ureter. Factors associated with the stone include size, location and the number of stones. However, factors linked with ureter are presence of mucosal edema, ureteric anatomy and peristalsis <sup>[6]</sup>. Conservative management may be complicated by intense colicky pain, hydronephrosis and urinary infection <sup>[7]</sup>. To avoid complications and accelerate stone passage, different medical treatments are in practice <sup>[8]</sup>. While managing lower ureteric stones, the most important advancement in recent years has been detection of role of expulsion therapy which

eases spontaneous expulsion of small ureteric calculi<sup>[9]</sup>. To ease spontaneous expulsion of distal ureteric calculi in adjuvant pharmacological medications like alpha blockers, calcium channel blocker, prostaglandins inhibitors and steroids are being used<sup>[10]</sup>. Another study has revealed that 71-98% of distal ureteric stones below the size of 5mm pass spontaneously whereas spontaneous expulsion rate is only 25-53% in stones measuring 5-10mm<sup>[10]</sup>. Furthermore, another study concluded that symptom duration more than 4 weeks increases the chances of complications from 7% to 20%. Stones smaller than 4mm are expelled in 1.6 weeks as compared to 2.8weeks which is the average time taken by the stones 4-6 mm. No stone more than 6mm passed spontaneously<sup>[11]</sup>.  $\alpha$ -blockers are of two types which are  $\alpha$ -1 and  $\alpha$ -2 blockers.  $\alpha$ -1 blockers are further divided into three subtypes.  $\alpha$ -1a receptors are located in bladder neck, prostate and posterior urethra whereas  $\alpha$ -1b receptors are present in the smooth muscles of the vessels. Detrusor muscle and lower ureter contain  $\alpha$ -1d receptors<sup>[12]</sup>. Ureteric  $\alpha$ -1 receptors inhibit smooth muscle tone and also decreases the amplitude and frequency of peristalsis. This decreases the intra-ureteric pressure. Urine exerts pressure above the calculus at the same time when intra-ureteric falls below it. This causes a suction effect which helps in stone progression and expulsion<sup>[6]</sup>. Non steroidal anti-inflammatory drugs have long been used in patients with renal colic because of their action on ureteral blood flow, smooth muscle, and edema<sup>[13]</sup>. In the setting of ureteral obstruction, renal blood flow increases initially resulting in increased collecting system pressure, an effect thought to be mediated by prostaglandins E2 and nitric oxide. NSAIDs inhibit the enzyme cyclooxygenase which is responsible for the synthesis of prostaglandins from fatty acids. Inhibition of prostaglandin production may reduce renal pelvic and ureteral pressure, promote relaxation of ureteral smooth muscle, and reduce ureteral edema. As such inhibition of prostaglandins synthesis may not only reduce the pain and obstruction associated with ureteral stone fragments but also increases stone expulsion rate. The provision of endoscopic instruments and experience of the

treating physician affects the treatment choice out of available options which could be watchful waiting, extracorporeal shock wave lithotripsy, intracorporeal lithotripsy using ureteroscope and ureterolithotomy<sup>[14]</sup>. None of the treatment options guarantees a stone free state. Although stone clearance is mainly dependent on size and location, there are some unmodifiable factors like ureteric anatomy and stone composition. Modifiable risk factors include smooth muscle spasm and mucosal edema which occurs due to stone impaction<sup>[15]</sup>.

### METHODOLOGY:

This randomized controlled trial was conducted at the department of Urology, Lahore General Hospital, Lahore for a period of 6 months i.e., from January 25, 2010 to June 24, 2010. Total 150 patients were selected using non-probability purposive sampling. Two groups were made i.e., group-A and group-B. 75 cases in each group were enrolled. All patients of age between 15-50 years from either gender, who presented in our department with single renal stone 5-20mm in size diagnosed on X - ray KUB were included in the study. However, patients having history of previous unsuccessful ESWL, concomitant use of calcium channel blockers or corticosteroids (on previous available medical record), previous history of pyeloureteral surgery, vertebral malformation, serum Creatinine > 1.5 mg/dl on labs, coagulopathy (PT > 2 seconds, APTT > 2 seconds, INR > 1.5), solitary functioning kidney or patient wishes for immediate stone removal were excluded from the study.

A total of 150 patients presenting in Urology OPD were enrolled for study as per inclusion and exclusion criteria. After full explanation of clinical trial and informed consent, patients were asked about their demographic profile. All patients divided into two groups using lottery method. Patients of group-A were given Cap. Tamsulosin 0.4mg just before sleep along with Tab. Diclofenac 50mg twice daily. The group-B only got Tab. Diclofenac 50mg Bid. All patients underwent ESWL every 3 weeks until procedure was efficacious or for 3 months, whichever was earlier. At the most total of four sessions of ESWL performed for each patient. ESWL was performed using a lithotripter of

electromagnetic variety i.e., Modulith –SLX-F-2, Storz Medical. ESWL was performed by a lithotripsy technician, under supervision of doctor from urology department. Treatment was continued until stone expulsion or until the need for auxiliary procedure. The primary end point was the stone clearance (as per operational definition), confirmed with the help of plain X-ray KUB performed after every three weeks before each session of ESWL. Data collected on pre-designed Performa by researchers. Quantitative variables like age were presented as mean±S.D. Whereas, qualitative variables like gender and efficacy were presented as frequency and percentage. The outcome variable i.e. stone expulsion was compared between the groups using Chi-square test. P= 0.05 will be considered significant. Data analysis was performed using SPSS v-11.

## RESULTS:

Total 150 patients were divided into two groups i.e., A and B. Mean age of the patients in group A was 33.97 + 10.50 years. Out of these, 16% (n=12) patients were 15-20 years of age, 24% (n=18) patients were 21-30 years, 29% (n=22) patients were 31-40 years and 31% (n=23) patients were 41-50 years of age (Table-I). Comparatively, group-B patients had the mean age of 35.32 + 10.46 years. 9% (n=7) patients were 15-20 years, 24 % (n=18) patients were 21-30 years, 36% (n=27) patients were 31-40 years and 31% (n=23) patients were 41-50

years of age (Table-I). Group-A had 57.3% (n=43) male patients as compared to 62.7% (n=47) in group B. Similarly, there were 42.7% (n=32) female patients were in group-A as compared to 37.3 % (n=28) patients. Patients were assessed for stone clearance in group-A, there were 38 (50.6%) patient in whom stone clearance was observed in first follow up at 3<sup>rd</sup> week, 10 (13.3%) patients in whom stone clearance was observed in second follow up at 6<sup>th</sup> week, 8 (10.6%) patients in whom stone clearance was seen at third follow up at 9<sup>th</sup> week, 9 (12%) patients in whom stone clearance was seen at fourth follow up at 12<sup>th</sup> week and no clearance was seen among 10 (13.4%) patients at the end of study. In group-B, 32 (42.6%) patients showed stone clearance at first follow up in 3<sup>rd</sup> week, 8 (10.7%) patients at second follow up in 6<sup>th</sup> week, 11 (14.7%) patients at third follow up in 9<sup>th</sup> week and 6 (8%) patients at fourth follow up in 12<sup>th</sup> week. In 18 (24 %) patients, no stone clearance was noticed at the end of study. Patients were distributed according to efficacy. In group-A, Tamsulosin was effective in 65 (86.6%) patients, while in 10 (13.4%) patients, it was not effective. Whereas only 57 (76%) patients of group-B were declared stone clear without the use of tamsulosin. In 18 (24 %) patients, there was no stone clearance (figure-I). The two groups were also compared for statistical significance of the results of stone clearance by chi-square test of statistics. The p-value was 0.094 showing not significant results.

**Table-I: Distribution of patients by age (n=150).**

Age in years	Group-A ( With Tamsulosin)		Group-B ( Without Tamsulosin)	
	No. of patients	Percentage	No. of patients	Percentage
15-20	12	16	7	9
21-30	18	24	18	24
31-40	22	29	27	36
41-50	23	31	23	31

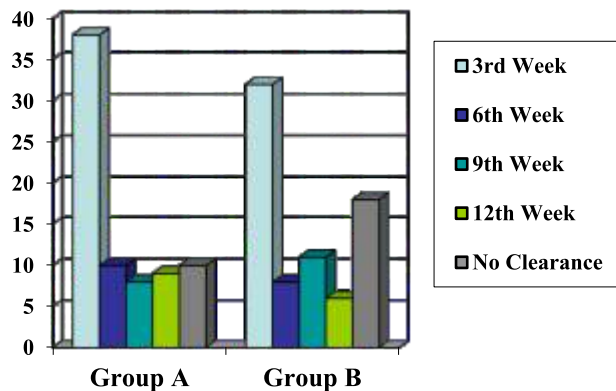
**Table-II: Distribution & comparison of patients by Efficacy in both groups (n=150).**

Efficacy	Group-A		Group-B	
	Number	%Age	Number	%Age
Yes	65	86.6	57	76
No	10	13.4	18	24

p-value =0.094

**Table-III: Efficacy at 3 weekly intervals.**

Weeks	Group-A Stone Clearance	Group-B Stone Clearance
3 <sup>rd</sup> week	50.6 %	42.6%
6 <sup>th</sup> week	13.3 %	10.7%
9 <sup>th</sup> week	10.6 %	14.7%
12 <sup>th</sup> week	12 %	8%



**Figure-I: Distribution of patients by Stone Clearance at follow up (n=150).**

**DISCUSSION:**

Recently, urological field has shown significant advancement e.g., ESWL and ureterorenoscopy which is commonly used in management of ureteric stones. However, these interventions are not risk free [6]. Kidney function significantly deteriorates if patient is kept on watchful waiting for longer duration. Different studies have shown that lower ureteric stones undergo spontaneous expulsion in 25-54% cases. However, it may require more than 10 days and considerable amount of analgesia [16]. Stones residing in the ureter cause colicky pain and non-visible hematuria. Invasive treatment is

indicated when there is visible hematuria, superadded infection or intractable pain. Transit of stone via ureter is controlled by many factors which are especially related to ureter and stone. Medical therapy is mostly aimed at modifying the ureteric factors. Many drugs have been used for this purpose which includes steroids, calcium channel blockers and alpha blockers. As ureteral smooth muscles have alpha-1 receptors, suggestion were made that blockade of these receptors may reduce ureteric peristalsis and thus facilitate stone passage. The clearance was achieved in maximum number of patients within first three weeks of therapy in our study. In other words prolonged use of tamsulosin did not help clear the stone as much as it did in early days of therapy. This study evaluated the tamsulosin in isolation for its efficacy in stone clearance. Yilmaz et al compared three different alpha blockers as a medical expulsion therapy in lower ureteric stones [17]. They divided 114 patients divided into four groups who received placebo, tamsulosin, terazosin and doxazosin. All patients were observed for 1 month. Expulsion rate in control group was 53.57%, in doxazosin group 75.86%, terazosin group was 78.57%, tamsulosin group was 79.31%. They found that all the alpha blockers are equally effective in enhancing spontaneous expulsion of distal ureteral stones and corticosteroid therapy may

not be necessary <sup>[18]</sup>. There are significant benefits of cost effectiveness of this therapy as compared to ESWL or ureteroscopy. Use of Tamsulosin as an adjunctive therapy has been studied by many researchers. In a randomized control trial, role of Tamsulosin was studied in 48 patients who underwent ESWL in distal ureteric stones measuring 6-15mm. Mean stone size in Tamsulosin group was 8.6 mm as compared to 8.2 mm in non-Tamsulosin group. After 15 days, the stone free rate was 70.8% and 33.3% in Tamsulosin and non-Tamsulosin group respectively ( $p=.019$ ). So, the investigators concluded that use of Tamsulosin therapy not only enhances stone clearance rate but also minimizes complication rate <sup>[16]</sup>. In the present study, 150 were divided into group-A (Tamsulosin) and group-B (without Tamsulosin). Each group had 75 patients. The patients in group-A, in which we used tamsulosin, demonstrated a higher stone passage rate as compared to group-B. In group-B stone passage rate at the end of study, was 76% as compared to 86.6% in group-A (Tamsulosin group). Stone clearance rate was statistically insignificant in Tamsulosin group.  $p$ -value was insignificant (0.094) but there was considerable difference in results in terms of efficacy. In group-A, 10.6% additional patients passed the stone fragmented when compared with group B. This difference in earlier stone clearance in both groups was also observed at 6<sup>th</sup> and 12<sup>th</sup> weeks. Stone clearance was observed to be highest among both groups in the first three weeks of therapy after ESWL, with 50.6 % efficacy in group A and 42.6% efficacy in group-B. The clearance gradually decreased in subsequent weeks, with more stone clearance rates in group-A, except for clearance at 9<sup>th</sup> week as compared to group-B (Table-III). As patients were followed, only 6 cases were observed with side effects in tamsulosin group but no patient stopped the drug due to side effects. In all these patients, main side effect was light headedness. None of the patients reported allergic reactions, fainting, palpitations or dizziness. In different studies patients with different stone size have been taken, maximum stone size being upto 10mm. In most studies observation period was up to 28 days. Stone clearance with conventional methods only, in international

studies at the end of three months is approximately 84.6%. While in this study we had clearance of fragments in 76% of patient's i.e. group-B (without the use of Tamsulosin). Stone clearance with use of tamsulosin (group-A) in international studies is approximately 94.1% while in this study we had stone clearance in 86.4% of patients using tamsulosin. Our results are comparable to international studies which are done on medical expulsion therapy of lower ureteric stones. The slight difference in results is probably due to difference in lithotripter used and better patient drug compliance in international studies.

### CONCLUSION:

Small renal stone fragments after ESWL should be managed conservatively to facilitate their passage through ureter. We have concluded that Tamsulosin therapy in distal ureteric stones did not make any statistical difference in terms of efficacy but still, there is considerable difference in stone clearance. It also decreases stone expulsion time. Based on comparison with international studies, we recommended alpha-1 antagonists to facilitate the passage of renal stone fragments after ESWL. Post-ESWL Tamsulosin therapy is a cheap option which improves patient satisfaction. But this drug needs to be further evaluated in our setup for its use in stone disease patients undergoing shockwave lithotripsy.

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**Author's Contribution**

**Nauman Khalid:** Study design, Manuscript writing & Proof reading.

**Aijaz Hussain Memon:** Over all supervision of data collection, Analysis and manuscript writing.

**Wasim Sarwar Bhatti:** Help in data collection & final draft of study.

**Hanan Noor:** Data Analysis & Manuscript writing.

**Muhammad Waqas Iqbal:** Manuscript writing.

**Muhammad Sohail:** Help in data collection.

**Asad Ramzan:** Data compilation and grammatical editing.

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