

# COMPARATIVE EFFECTIVENESS OF TAMSULOSIN VERSUS STANDARD MEDICAL THERAPY FOR MEDICAL MANAGEMENT OF SMALL URETERIC STONES

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 Date Received: October 01, 2017  
 Date Revised: July 16, 2018  
 Date Accepted: July 27, 2018

## ABSTRACT

**Objective:** To investigate and compare the effectiveness of tamsulosin versus standard medical therapy (SMT) for conservative management of ureteric stones in terms of time needed for stone expulsion, reduction in pain episodes and stone expulsion rates.

**Methodology:** This was a prospective non-blinded, non-randomised controlled study conducted at Urology Unit, LRH Peshawar, from July 2015 to June 2016. 50 patients were included, 25 patients in Group 1 (SMT) and 25 patients in Group 2. All patients were selected consecutively from the outpatient department with a stone size  $\leq 10$  mm. In Group 1, patients were prescribed adequate oral analgesics while Group 2 patients were given tamsulosin plus analgesics for pain relief on as need basis. Data was obtained about symptoms duration, stone size, stone location, total pain episodes and the time to passage of stone.

**Results:** There were 35 (70%) males and 15 (30%) females with a ratio of 2.3:1. Overall mean age was  $31.84 \pm 5.64$  years; range was 22 to 42 years; and mean duration of symptoms was  $6.64 \pm 1.48$  days. The overall mean stone size was  $5.94 \pm 1.46$  mm (range 4 mm to 9 mm). Significant differences were detected in total pain episodes (mean pain episodes for group 1= 3.64 & group 2= 1.6,  $p < 0.0001$ ) and stone passage time (mean passage time for group 1=  $17.52 \pm 7.22$  days & group 2=  $10.44 \pm 5.64$  days,  $p < 0.0001$ ).

**Conclusions:** Tamsulosin effectively reduce the time needed for spontaneous expulsion of ureteric stones. It increases the rate of stone passage and importantly reduces the number of pain episodes.

**Key Words:** Tamsulosin, Ureteric stones, Medical expulsive therapy

This article may be cited as: Khan A, Ahmad T, Khan I, Khattak IU. Comparative effectiveness of tamsulosin versus standard medical therapy for medical management of small ureteric stones. *J Postgrad Med Inst* 2018; 32(3): 256-61.

## INTRODUCTION

Renal tract stones are known to mankind for millennia. They are associated with considerable morbidity and if untreated can lead to obstructive renal failure<sup>1</sup>. The lifetime prevalence in the Middle Eastern countries is estimated at 20-25% as compared to the 5-10% prevalence in western communities. Men (124 per 100,000) are several times more affected than women (36 per 100,000)<sup>2,3</sup>. Moreover, the recurrence rate ranges between 50-80% during a 10-year period<sup>4</sup>.

The majority (97%) of renal tract stones are encountered in the ureter and kidneys while 3% are found in the bladder and urethra<sup>4,5</sup>. A number of treatment methods have been evaluated in the medical literature,

ranging from conservative watchful waiting<sup>6</sup>, laser<sup>7</sup> and shockwave lithotripsy<sup>8</sup> to invasive procedures like laparoscopic<sup>9</sup>, endoscopic or open procedures<sup>10</sup>. Most of these procedures are indicated depending primarily upon factors contributed by the stone, anatomy of the renal tract, comorbidities, personal preferences or a combination of these<sup>11,12</sup>.

Medical expulsive therapy (MET) for ureteric stones has recently received a reappraisal among the medical and conservative options during the initial 6 weeks of presentation<sup>13</sup>. Studies have shown that MET effectively reduces the time to passage of the stone while also reducing the number of colic episodes<sup>12-14</sup>. MET is also dependent upon the size of the stone ( $\leq 10$  mm) and renal tract anatomy as well as the preference of the patient.

It has also been suggested that smaller stones ( $\leq 5$  mm) have higher rates of expulsion (75-80%) with MET while stones between 5 to 10 mm size have moderate rates of passage (45-50%)<sup>14</sup>. The Canadian Urological Association (CUA) guidelines<sup>15</sup> for ureteric stone management states that MET should be considered as a viable option in stones  $\leq 10$  mm in order to shorten the passage interval and pain episodes. However, they have cited a large randomised controlled trial by Pickard et al<sup>16</sup> where they have concluded that MET does not reduce the need for additional therapies for stone retrieval. Similarly, other studies have also concluded that MET might not be helpful or altogether useless<sup>17</sup>. On the other hand, large reviews of RCTs have shown that MET is highly effective in at least shortening the passage interval and pain episode<sup>13,15</sup>. In order to find answers for the currently ongoing controversy regarding MET, especially the use of tamsulosin versus conservative therapy, we aimed to conduct a prospective study where we hope to determine the effectiveness of MET as compared to SMT. The role of tamsulosin is to increase the rate of expulsion of small ureteric stones and will be thus benefitting the patients presenting with severe renal colic.

## METHODOLOGY

This was a prospective non-randomised study conducted at Urology Unit, LRH Peshawar, from July 2015 to June 2016. The institute's ethical committee approval was obtained before commencing the study. Informed consent was taken from all patients before inclusion in the study. After thorough clinical assessment the patients were investigated with ultrasonography of the renal tract. Stone size & location were determined using high frequency ultrasonic probe. All other relevant investigations were ordered from the hospital laboratory such as full blood counts, urea & creatinine, serum electrolytes and urine microscopy.

Two treatment arms were created; group 1 and group 2. Patients in group 1 were prescribed with analgesics (diclofenac sodium 50 mg TID) with gastroprotection (oral ranitidine 150 mg BID). Patients in group 2 were prescribed with analgesics and gastroprotection as for group 1, but additionally they were prescribed with Tamsulosin (400  $\mu$ g once daily in the morning). Patients who presented with concomitant features of urinary tract infection (UTI) were also treated with antibiotics (ciprofloxacin 500 mg BID) in both groups. Fifty patients with age 16 or above having small primary ureteric stone of size 1-10 mm were included in the study. While patients having abnormal renal function tests, severe complicated UTI or evidence of moderate to severe dilation of the renal tract (ureter, pelvis, kidney) on ultrasonography were excluded. All patients were followed-up for 4-week time (28 days), with complete clinical and ultrasonographic assessment of the stone

position or presence/absence thereof, every week in the outpatient department. Data was collected about patient demographics such as age, gender & comorbidities. Symptoms duration was noted along with ultrasonographic location and size of the stone along the ureter. Parameters recorded during follow-up were status of the stone (passed/not passed), time to stone passage (in days/weeks), total pain episodes, hospitalisation (if required) and complications of the drug treatment as well as the stone. All patients who failed to pass stone during the study period or who developed severe complications due to ureteral stones were managed according to their clinical findings.

The data was coded and entered in a digital chart. At the conclusion of the study, the data was imported to SPSS version 22.0. Qualitative data was presented in frequencies and percentages while continuous data was presented as mean  $\pm$ SD. Analysis was done for all the predictor and outcome variables (mean total pain episode, mean stone passage time, stone passage rate and complications) and the data was stratified according to treatment method given. The Shapiro-Wilk test and the Smirnov-Kolmogorov tests were used to assess the normality of the available data before applying special tests. An independent samples t-test was used to ascertain mean difference between the predictor and outcome variables according to the treatment given. In case assumptions for the parametric tests were violated, a Mann-Whitney U test was conducted to ascertain a statistically significant difference. In all tests a p-value of  $\leq 0.05$  was considered significant.

## RESULTS

There were 35 (70%) males and 15 (30%) females with a ratio of 2.3:1. Overall mean age was  $31.84 \pm 5.64$  years; range was 22 to 42 years; and mean duration of symptoms was  $6.64 \pm 1.48$  days. The overall mean stone size was  $5.94 \pm 1.46$  mm (range 4 mm to 9 mm). There were no cases with concomitant major comorbidities, neither was any patient lost to follow-up during the 4-week period. 20 (40%) stones were found in the upper one third of the ureter at the time initial scan, 15 (30%) in the mid-third while 15 (30%) stones were found in the lower one third of the ureter. Complications reported were of minor degrees and none required discontinuation of treatment. (Table 1)

In group 1, mean age was  $33.68 \pm 5.5$  years, 18 (72%) were males and 7 (28%) were females with a mean symptoms duration of  $6.24 \pm 1.45$  days. The mean stone size was  $6.12 \pm 1.54$  mm. 10 (40%) stones were encountered in the upper one third, 8 (32%) in middle one third and 7 (28%) in the lower one third. The stone passage status (passed/not-passed), mean stone passage time in days, mean total pain episodes and complications for group 1 are listed in Table 1 & Table 2. In group 2, mean

**Table 1: Treatment-group wise outcome**

Clinical Variable	Group 1 (SMT)	Group 2 (MET)	Significance
Mean Total Pain Episodes	3.64 ± 0.995	1.60 ± 0.707	P <0.0001
Mean Stone Passage Time (days)	17.52 ± 7.23	10.44 ± 5.64	P <0.0001
Stone Passage Rate (N, %)	19 (76%)	23 (92%)	P = 0.24
Complications			
Nasal Congestion (N, %)	None	3 (12%)	
Postural Hypotension (N, %)	None	2 (8%)	
Sexual Dysfunction (N, %)	None	2 (8%)	
<b>SMT:</b> Standard Medical Therapy; <b>MET:</b> Medical Expulsive Therapy			

**Table 2: Expulsion rates for the two treatment arms**

Time	Group 1: n (%)	Group 2: n (%)
Week 1	3 (12%)	8 (32%)
Week 2	8 (32%)	12 (48%)
Week 3	10 (40%)	3 (12%)
Week 4	4 (16%)	2 (8%)

**Table 3: The independent samples t-test for comparison of mean difference between the two treatment groups**

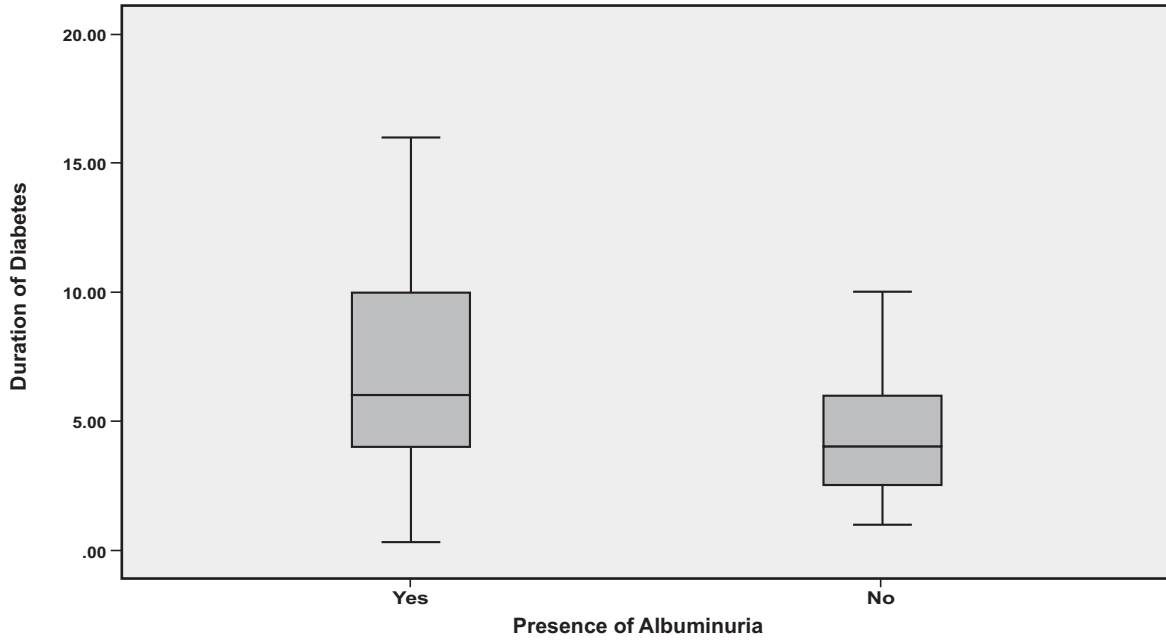
Clinical Variable	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI of Difference	
						Lower	Upper
Patient Age	2.418	48	0.019	3.680	1.522	0.620	6.740
Symptoms Duration	-1.964	48	0.055	-0.800	0.407	-1.619	0.019
Stone Size	0.868	48	0.390	0.360	0.415	-0.474	1.194
Pain Episodes	8.356	48	<0.0001	2.040	0.244	1.549	2.531
Stone Passage Time	3.860	45.328	<0.0001	7.080	1.834	3.387	10.773

age was 30 ±5.25 years, 17 (68%) were males and 8 (32%) were females and mean symptoms duration was 7.04 ±1.43 days. Mean stone size was 5.76 ±1.93 mm. Stone location was as follows; 10 in upper one third, 7 in the middle third and 8 in the lower third of the ureter. Rest of the outcome variables are shown in Table 1 & Table 2.

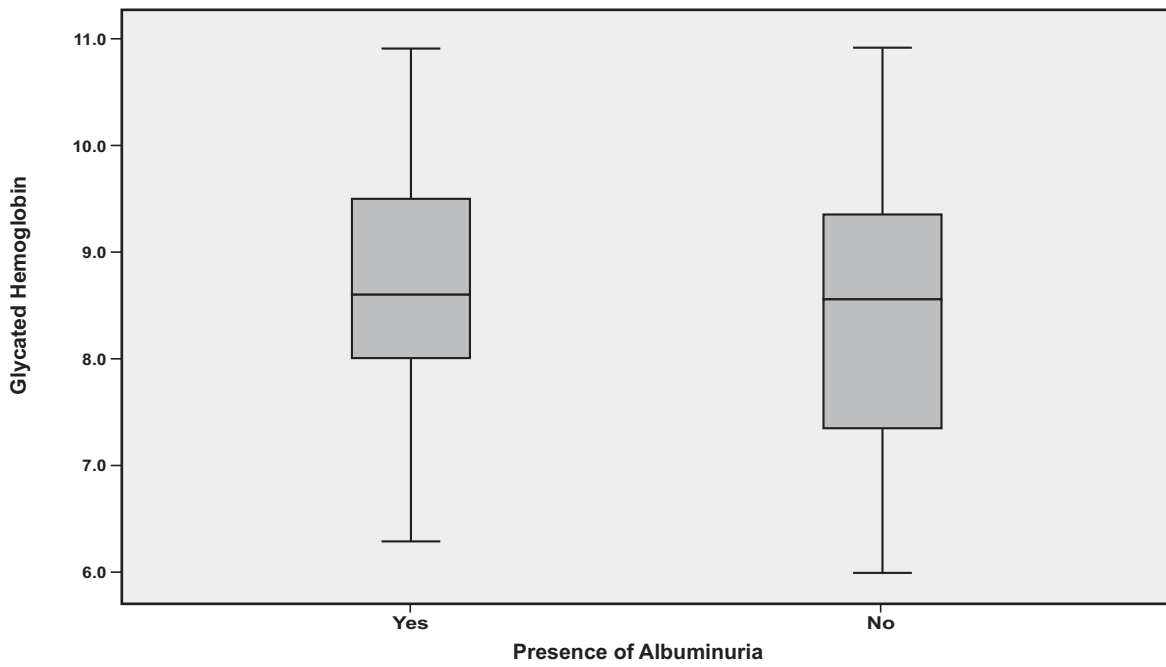
There were no outliers in the data, as assessed by inspection of a boxplot. Stone passage rates for each treatment group were normally distributed, as assessed by Shapiro-Wilk's test ( $p > .05$ ), and there was no homogeneity of variances, as assessed by Levene's test

for equality of variances. There were no significant differences in stone sizes or pain duration between the treatment groups. Significant differences were detected in total pain episodes (mean pain episodes for group 1= 3.64 & group 2= 1.6,  $p < 0.0001$ ) and stone passage time (mean passage time for group 1= 17.52 ±7.22 days & group 2= 10.44 ±5.64 days,  $p < 0.0001$ ) as is shown in Table 2, Figure 1 & Figure 2. Distributions of the passage rates for group 1 and group 2 were not significantly different for the two treatment groups. Passage rates for group 1 (mean rank= 27.50) and group 2 (mean rank= 23.5) were not significantly different,  $U = 262.50$ ,  $z = -1.528$ ,  $p = 0.13$ .

**Figure 1: Mean stone passage time for the two treatment groups**



**Figure 2: Total pain episodes representation between the treatment groups**



## DISCUSSION

Ureteric stones bear significant morbidity due to its high prevalence and occurrence in younger age population<sup>13</sup>. Such a high prevalence of morbidity due to stones warrant particular focus in establishing effective, rapid and financially affordable treatment methods. The most significant effects of MET are to shorten the stone passage time and to reduce the number of pain episodes till the stone is cleared. Our main aim was to analyse these two variables. We therefore noted a significant effect of MET on the duration of stone expulsion as compared to SMT (mean difference= 7.08 days, 95% CI, 3.387 to 10.773,  $p < 0.0001$ ). These findings are concurrent with the findings of numerous randomised studies<sup>6,19-21</sup>. A large Cochrane database review by Campschroer et al<sup>19</sup> has shown that MET significantly reduces stone expulsion time as well as the number of pain episodes. The CUA guidelines<sup>15</sup> recommend that MET must be primarily used to shorten stone passage interval and reducing the number of pain episodes. Reduction in the number of pain episodes translates into lesser requirement for oral or parenteral analgesia and reduced number of A&E visits<sup>22</sup>.

We included adult patients with primary episodes of colic and radiologically proven location within the ureter. We, however, taken in consideration all locations of stone within the ureter. Many studies have shown the efficacy of MET in distal ureteric stones with primary aim of improving stone expulsion rates. Ahmad et al<sup>23</sup> has shown an effective stone expulsion rate of more than 85% for tamsulosin group while only 55% rate for patients without tamsulosin treatment. Other features of this study are also in agreement with our study where majority (73.46%) of stones in MET group were cleared during the first two weeks of start of treatment whereas only 30% of stones in control group passed during the first two weeks<sup>23</sup>. In our study, about 44% of stones were passed during the initial 14 days for SMT whereas 80% of stones passed in the MET group during the same period ( $p < 0.0001$ ). This shows that the benefits of MET are consistent across studies from our country and MET is an effective mode of treatment for small stones. However, it is very important to note that the primary aim of MET should be reduction of time needed for stone expulsion rather than expulsion rate itself.

In a randomised controlled trial, Zehri et al<sup>18</sup> showed stone expulsion rate of 70% during the initial week after treatment while the control group only achieved 37% expulsion rate<sup>18</sup>. These findings are also concurrent with our findings, except that we included stone location from all sites of ureter while these above mentioned studies have taken into account only the distal ureteric stones.

In a recent study by Ahmed et al<sup>12</sup> several predictive factors have been described which may be used to prognosticate the spontaneous passage of ureteric stones. These factors were high pain scores, stones  $\leq 5$  mm, lower ureteric stone, high white cell counts and those without perinephric fat stranding on CT scan<sup>12</sup>. However, they have shown that only 15% of stones passed during the initial two weeks without any treatment which is a quite low expulsion rate<sup>12</sup>. In another prospective study by Ibrahim et al<sup>14</sup>, pain duration, haematuria, stone surface regularity and degree of obstruction. They showed that duration of pain if less than 30 days was the only significant factor which predicted successful passage of stone without any treatment<sup>14</sup>. However, they have stated that in stones  $>10$  mm in size, these factors do not have any prognostic role<sup>14</sup>. We studied the effects of symptoms duration on passage time and did not find any correlation between the two (Spearman's R2: -0.18,  $p = 0.21$ ). However, it is important to note that stone size had negative correlation with duration of symptoms (R2: -0.029,  $p = 0.84$ ). It was also noted that stone location within the ureter did not have any association with the expulsion rate ( $p = 0.57$ ,  $Z = -0.56$ , Mann-Whitney  $U = 148$ ).

One of the negative effects of alpha blockers are their systemic effects such as retrograde ejaculation, nasal congestion and postural hypotension. Though we noted these complications in a minority of our patients, they should be kept in mind, and if significantly affecting lives of the patients, alpha blockers should be withdrawn or replaced with another agent. Ibrahim et al<sup>19</sup> in a prospective RCT found side effects of tamsulosin in 13% of patients while 15% of patients with alfuzosin had these side effects<sup>19</sup>. As mentioned earlier, these side effects did not lead to stopping of the MET as they were of minor degree. Randomised clinical trials with larger sample sizes are required to effectively answer questions regarding MET.

## CONCLUSION

Small ureteric stones can be easily managed using medical expulsive therapy by utilising the specific alpha1 blocking agents. The most significant effect of this therapy was shortening of time to stone expulsion and decrease in the number of pain episodes. Stone expulsion rates remains the same across conservative therapy and medical expulsive therapy.

## RECOMMENDATIONS

We recommend to consider MET in all patients with ureteric stones of  $\leq 10$  mm, especially those who want to opt for medical management. Moreover, MET should not be limited to distal ureteric stones only, unless the stones are too large and/or the renal tract is significantly dilated or there are high chances of renal damage.



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## CONTRIBUTORS

AK conceived the idea, planned the study and drafted the manuscript. TA, IK and IUK helped acquisition of data, did statistical analysis and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.