ROLE OF TAMSULOSIN IN UPPER URETERIC STONES A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Background: Twenty percent of the population is affected by renal stone disease. Treatment include conservative management, shockwave lithotripsy, percutaneous nephrolithotomy (PCNL), endourological retrieval and open surgery. Controversy exists regarding the role of tamsulosin as the agent for medical management of small stones without obstruction.

Objective: We aim 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.

Methods: This is a prospective randomised controlled study conducted between January 2016 and December 2016. We included 110 patients, 57 for group 1 (tamsulosin) and 53 for group 2 (standard medical therapy). Patients with single upper ureteric stone of ≤10 mm, presenting with acute colic and confirmed with ultrasound and X-Ray KUB were included. Data for both treatment groups was compared for pain scores, time to spontaneous stone passage, pain episodes and adverse effects from the treatment.

Results: Of the 110 patients, there were 79 (71.8%) men and 31 (28.2%) women with a mean age of 32.5 ± 5.6 years (22-42 years). For group 1, the total stone expulsion rate was 78.9% (n = 45) while for group 2, it was 64.2% (n = 34). This stone expulsion rate for the two treatment groups was statistically significant as shown by the independent samples t-test with a mean difference in stone clearance time of -4.9 days (95% CI: -7.32 to -2.55, p <0.0001) as the mean stone expulsion time for group 1 was 12.6 ± 6.8 days while for group 2 it was 17.5 ± 5.7 days.

Conclusions: Medical expulsive therapy using analgesia with tamsulosin is effective in clearance of upper ureteric stones. It also reduces the severity and number of colic episodes as well as reducing the need for oral and parenteral analgesics.

Keywords: Upper ureteric stones, tamsulosin, medical expulsive therapy.

INTRODUCTION

Ureteric stones are a cause of pain and suffering for a considerable proportion of the population with an attendant risk of obstructive uropathy and renal failure.[1] In Asia, lifetime prevalence is in the range of 20% to 25% where men are affected more than women (124 per 100,000 vs 36 per 100,000).[2,3,4] 97% stones are encountered in the ureter and kidneys while only 3% are found in bladder and urethra.[4,5] Various modality of treatments for renal calculi range from watchful waiting[6], LASER[7] and shockwave lithotripsy[8] to invasive procedures like laparoscopic[9], endourological or open procedures.[10] The decision for any of these procedures depend on several factors such as stone size, location, local anatomy, comorbidities and patient or surgeon preferences.[11,12]

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Medical management for ureteric stones is a viable option during the first 6 weeks of presentation in the absence of any conditions which warrant urgent intervention.[13] Numerous studies[12,13,14] have shown that alpha-blocker especially tamsulosin, reduces time to stone passage, reduce colic episodes and intensities. Size of the stone is an important determinant in medical expulsive therapy (MET) and most series have included cases with maximal stone diameter of 10 mm or less.[14] However, despite some studies showing benefit for stone expulsion[15], other studies have questioned its efficacy. A large multicentre trial from the United Kingdom, Pickard et al[16] has shown that MET is equal to placebo, and on the expense of severe adverse effects. They raised serious questions on the methodological faults of studies showing favourability of MET.[17] However, most of the studies report expulsion rates for lower ureteric stones while studies on proximal ureteric stones are limited.

We aimed to conduct a randomised study where we can study the effectiveness of MET in enhancing upper ureteric stone expulsion and its effect on reducing the number and severity of pain episodes. Consequently, it will enhance evidence base for the selection of MET in patients with upper ureteric stones.

METHODS

Prospective randomised study of twelve month duration (January 2016 to December 2016) conducted at the department of Urology MTI Lady Reading Hospital, Peshawar. Approval was obtained from the ethical review committee of the institute. Informed consent was obtained from all patients at the inclusion in the study according to declaration of Helsinki.

Patients were included from the OPD and emergency clinics of the institute. All patients between age 18 and 65 years from both genders with acute ureteric colic and ultrasound, X-Ray KUB evidence of upper ureteric stone of ≤10 mm diameter were included. Patients with moderate to severe (grade 3 and 4) hydronephrosis, those with deranged serum renal function tests, severe comorbidities precluding the use of drugs under study and those who did not consent for inclusion in the study were excluded. Two treatment groups were created; Group 1 and 2. Patients who were treated with standard medical therapy (SMT) plus tamsulosin 400 μg once daily were included in group 1 and patients who were only given SMT were included in group 2.

SMT was defined as best medical management with analgesics (Paracetamol 1g TDS, Diclofenac 50 mg TDS, Ranitidine 150 mg TDS) or according to symptom onset intramuscular injection of diclofenac sodium 75 mg. Initially we included 120 patients, 60 for each study group, however, during the course of the study 3 patients from group 1 and 7 patients from group 2 were excluded due to loss to follow-up. The study protocol included follow-up of patients bi-weekly for 4 weeks. At the end of the 4 weeks, data was collected about pain scores according to the visual analogue scale, number of colic episodes and whether they passed the stone.

The primary end-point of the study was spontaneous stone passage within the 4 weeks period. Failure of medical therapy was failure to pass stone within the 4 weeks period or if a patient opted for another treatment modality. Data was entered and analysed using SPSS version 22.0. An independent samples t-test was run to ascertain mean difference for time to stone passage for both groups while Chi-square test was used to determine association between variables. Difference for time trend for groups was also analysed using the Kaplan-Meier survival distribution curve with log-rank test.

RESULTS

Of the 110 patients, there were 79 (71.8%) men and 31 (28.2%) women with a mean age of 32.5 ± 5.6 years (22-42 years). The mean symptoms duration was 6.5 ± 1.5 days (range: 3-9 days). Overall mean stone diameter was 6.6 ± 1.8 mm (range: 4-10 mm). Mean visual analogue score (VAS) was 7.6 ± 0.9 (range: 5-9)

Table 1: Descriptive statistics for the 2 treatment groups with mean difference, 95% confidence intervals and p values from independent samples t-test

Variable	Tx Group	n	Mean	SD	P value	MD	95% CI
Patient age	Tamsulosin	57	33.60	5.7	0.062	2.1	0.075 to 4.25
	Control	53	31.43	5.4			
Symp. Duration	Tamsulosin	57	6.25	1.4	0.060	-0.53	-1.08 to 0.02
	Control	53	6.77	1.5			
Stone size	Tamsulosin	57	6.60	1.8	0.93	-0.03	-0.69 to 0.64
	Control	53	6.62	1.8			
VAS pre-treatment	Tamsulosin	57	7.51	1.04	0.538	-0.114	-0.48 to 0.25
	Control	53	7.62	0.98			
VAS post-treatment	Tamsulosin	57	2.86	1.3	<0.0001	-1.07	-1.61 to -0.519
	Control	53	3.92	1.6			
Paracetamol	Tamsulosin	57	1020.18	364.6	<0.0001	-386.4	-540.3 to -232.5
	Control	53	1406.60	448.0			
PO Diclofenac	Tamsulosin	57	17.98	25.8	<0.0001	-42.9	-52.9 to -32.8
	Control	53	60.85	27.5			
Total pain episodes	Tamsulosin	57	3.30	0.99	<0.0001	-2.5	-2.9 to -2.1
	Control	53	5.81	1.35			
Stone passage time	Tamsulosin	57	12.60	6.8	<0.0001	-4.9	-7.3 to -2.5
	Control	53	17.53	5.7			

Tx group = treatment group
n = sample size
SD = standard deviation
MD = mean difference
95% CI = 95% confidence interval
VAS = visual analogue score

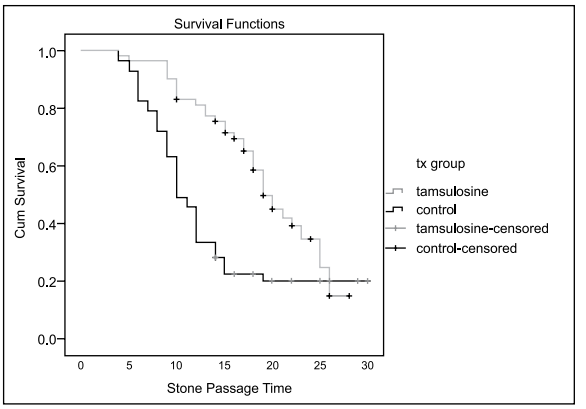

Figure 1: Kaplan-Meier curves for the two treatment groups

and mean overall VAS at day 14th was 3.4 ± 1.5 (range: 1-8). The overall mean paracetamol dose was 1206.3 ± 449 mg/day, mean diclofenac sodium dose was 38.6 ± 34.1 mg/day. The median number of episodes were five within 4 weeks follow-up. The mean stone passage time was 14.9 ± 6.8 days. There was no statistically significant difference for age, symptoms duration, stone size and preoperative VAS scores as shown by independent samples t-test. Table 1

For group 1, the total stone expulsion rate was 78.9% (n = 45) while for group 2, it was 64.2% (n = 34). This stone expulsion rate for the two treatment groups was statistically significant as shown by the independent samples t-test with a mean difference in stone clearance time of -4.9 days (95% CI: -7.32 to -2.55, p <0.0001) as the mean stone expulsion time for group 1 was 12.6 ± 6.8 days while for group 2 it was 17.5 ± 5.7 days. Post-treatment VAS scores did show statistically significant difference with a mean difference of -1.1 (95% CI: -1.6 to -0.52, p<0.0001) where mean VAS for group 1 was 2.9 ± 1.3 while for group 2 was 3.9 ± 1.6. Comparing the number of colic episodes, it was found that mean number colic episodes were significantly lesser for group 1 (mean: 3.3 ± 0.9) as compared to group 2 (5.8 ± 1.3) with a mean difference of -2.5 (95% CI: -2.9 to -2.1, p<0.0001). Additionally, for group 1 there were only 8 (14%) patients who presented to the emergency department with severe colic not controllable with oral medications, and they need parenteral analgesics. Conversely, for group 2, 21 (39.6%) patients presented to the emergency department with severe colic requiring parenteral analgesia (Pearson Chi-square = 9.26, p = 0.002).Table 1

When data was analysed regarding the passage rates for stone size subgroup, it was observed that stone size did affect the passage rates. There were 38 stones with ≤5 mm diameter while there were 72 stones with ≥5 mm diameter. Thirty-four (89.5%) stones with size 5 mm or less cleared within the study period while 45 (62.5%) stones cleared in the ≥5 mm diameter group (Pearson Chi-square = 8.9, p = 0.003). 6 (50%) of the 12 patients in group 1 and 7 (36.8%) of the 19 patients in group 2 who failed to expelled but relocated to lower or middle third, the stones were retrieved with ureteroscopy. For remaining cases in both groups, who failed to relocate the stones, we used shockwave lithotripsy.

The side effects in both groups were compared. Tamsulosin treatment was significantly associated with 29.8% (n = 17) cases of headache, 17.5% (n = 10) cases of orthostatic hypotension, 15.8% (n = 9) cases of nasal congestion/rhinitis and 3.5% (n = 2) cases who reported ejaculatory problems. Gastric upset in tamsulosin group was reported in 6 (10.5%), diarrhoea in 8 (14.0%) and dizziness in 7 (12.3%) of cases. On the other hand, in group 2 gastric upset was reported in 9 (17%), diarrhoea in 12 (22.6%) and dizziness in 9 (17%) of cases. No patient reported stopping the medications due to side effects.

Time taken to stone passage was also analysed using the Kaplan-Meier survival curve in order to test for the difference between the two treatment groups. It is shown in Figure 1 that patients who took tamsulosin passed the stones early as compared to those who did not. A log rank test was conducted to determine if there were differences in the survival distributions for the two treatment groups. The survival distributions for the two groups were statistically significantly different ($\chi 2$ (1) = 10.5, p = 0.001).

DISCUSSION

Fisang and associates[5] estimated that renal calculi are the second most common presentation in urology clinic after prostate disease, while Zehri and associates[18] has shown that renal stone management involves 40% to 50% of workload in Pakistan.[5,18] It would be of high clinical value, if non-invasive and affordable medical management is proven effective. The American Urological Association, European Association of Urologists and the Canadian Urological Association (CUA) have recommended that MET be considered for ureteric stones in order to expedite stone passage.[15]

Shortening of time to stone passage is achieved by the use of tamsulosin, bringing down colic episodes and severity of pain. Our study analysed tamsulosin effects on passage rates of upper ureteric stones. The effects were not much different from other locations of ureteric stones since the time to stone expulsion, number of colic episodes, total analgesic dose, number of admissions with intractable pain and severity of each episode of colic were reduced significantly in comparison to conventional best medical management. Findings of our study are in agreement with multiple randomised studies.[6,19,20,21] Campschroer and co-workers[19] in a systematic review have shown that tamsulosin reduces time to expulsion of the stone as well as the number of pain episodes. Tamsulosin has been recommended by the CUA[15] in their published guidelines for ureteric stone man-

agement. Lesser analgesic dose and lower number of emergency visits are the primary reason which improves health outcomes.[22]

Researchers have primarily focussed on the distal ureteric segment and have reported the presence of α1-receptors. However, recently it was reported that these receptors are present on the proximal part of the ureter as well.[23,24] Davenport and co-workers[25] demonstrated that application of tamsulosin lowered intraluminal pressure in the entire ureter and not just the distal ureter. Spontaneous stone passage is higher from the lower ureter, however, it is easily predictable that the use of tamsulosin will also enhance the passage of upper ureteral stones. Watts et al[26] in a prospective study showed that tamsulosin has a positive effect on stone passage regardless of stone location while those without tamsulosin usage had lower rates of stone passage. Yencilek et al[27] in a randomised controlled study evaluated the stone clearance rates for upper ureteric stones. They showed that stones with a diameter of 5 mm or less were more likely to be expulsed than those greater than 5 mm. In our study, we also noted the same effect of stone size, where more stones with size ≤5 mm were expulsed spontaneously (89.5%) as compared to stones ≥5 mm size (62.5%) and this association of stone size and passage rate was statistically significant ($p = 0.003$). However, it is noteworthy that the time to stone passage is independent of the size of the stone and we did not find any difference between the groups ($p = 0.12$) neither does it affect the number of colic episodes ($p = 0.79$).

Ahmad and co-workers[28] have shown 85% stone expulsion rate for tamsulosin as compared to 55% of the control group. Majority of stones in this study were cleared during the second week while only 30% of stones were cleared during the first week.[28] In our study,the overall stone clearance was 39.1% during the second week while only 12.7% passed during the first week. Similarly, for tamsulosin group 52.6% of stones were cleared during the second week which was 24.5% for the control group ($p<0.0001$).

Zehri AA et al[18] in a randomised trial found stone expulsion rate of 70% in the first week while it was 37% during second week.[18] These findings are in agreement with our study except that we included upper ureteric stones in the analysis while most other studies have reported middle and lower ureteric stones. Despite some studies reporting no evidence of the benefit of tamsulosin for ureteric stone expulsion, it is imperative to say that numerous studies have demonstrated the positive role of tamsulosin in stone expulsion despite the location of stone in the ureter. It should be recommended for patients who present with smaller stones (≤10 mm) and without derangements of renal functions or infection.

Ibrahim and colleagues[19] in a randomised study noted side of effects of tamsulosin in about 13% of patients, most common of which were headache and orthostatic hypotension.[19] They, however, reported that no patient stopped treatment due to side effects. The adverse effects of tamsulosin are a matter of concern for many urologists. In our study, headache (29.8%) and orthostatic hypotension (17.5%) were the most common adverse effects of the therapy but none of the patient discontinued their treatment due to their side effects. Other than that, gastric upset, dizziness and diarrhoea are common with the nonsteroidal anti-inflammatory drugs and their incidence was not different between the two groups. We recommend that patient should be educated about possible episodes of headache or orthostatic hypotension and tasks that involves continuous concentration should be avoided.

CONCLUSIONS

Upper ureteric stones are commonly associated with severe colic episodes. Medical expulsive therapy using analgesia with tamsulosin is effective in clearance of upper ureteric stones. It also reduces the severity and number of colic episodes as well as reducing the need for oral and parenteral analgesics. It should be offered to patients with less than 10 mm stones in the upper stones, who otherwise have no contraindications for the drugs or impaired renal functions waranting other modalities of stone retrieval.

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