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Efficacy of Tamsulosin Alone and Combination with Tolterodine in Managing Intramural Ureteric Stone

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ABSTRACT

Objective: To compare the efficacy of Tamsulosin alone and combination with in managing intramural ureteric stone in order to obviate the need for surgical treatment and related complications

Methodology: The study was conducted in Federal Government Polyclinic Hospital (polyclinic hospital), PGMI, Islamabad from October 2017 to March 2018. A total of 104 patients with distal ureteral stones were included in the study (90 men and 14 women) age ranging from 19 to 59 years. After randomization, divided 2 groups and patients were given respective drugs. Group 1 patients received Tamsulosin 0.4 mg/day, group 2 patients received Tamsulosin 0.4 mg/day plus 2 mg (twice a day).

Results: The mean days of stone expulsion was 20.05± 6.11 and 10.41±4.63 days in group 1 and 2, respectively which was significantly shorter in group 2 (p-value, <0.001). Overall in 43 (82.6%) patients in group 2 and 34 (65.3%) cases in group 2, stone was expulsed before 28 days. The expulsion of intramural ureteric stones were more observed in patients treated with combination therapy (group 2) than tamulosin alone therapy. The mean duration of expulsion of stones was also found significantly shorter the combination therapy group.

Conclusion: In the present study, the expulsion of intramural ureteric stones were more observed in patients treated with combination therapy (group 2) than tamulosin alone therapy. It is concluded that Tamsulosin combined with has a better effect in terms of intramural ureteric stone expulsion.

Keywords: Tamsulosin, Tolterodine, ureteric calculi, medical expulsive therapy.

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Introduction

Pain due to ureteric stones is the commonest complaint in urology emergency. Many management choices are presented for cure including both surgical and medical therapy. Medical management includes the drugs that facilitate the smooth expulsion by controlling pain, inflammation and edema and by relaxing the smooth muscle of ureter. The resolution of this trail is to measure the comparative usefulness of the two non-invasive conservative drug management for intramural ureteric stone management in order to obviate the need for surgical treatment, surgical procedure related complications, morbidity, anesthesia risks and to reduce hospital expenditure.

Urolithiasis is prevalent in 12(8-15)% of the total population. In Asia, the worldwide rate of the disease has been expressed to be around 6.8% in males and 14.6 % in female population.[1] After the disease identification, its mean rate of reoccurrence is 75% in 20 years. In Pakistan, the recurrence of the disease changes between 200 cases for each 100,000 in the south to 2.4 per 100,000 individuals in north.[2]

20% of urolithiasis occurs in ureters out of which 70% are found to be present in distal ureters. Due to advancement in minimally invasive or endoscopic surgical techniques and advancements in intra-corporeal lithotripters, significant development has been seen recently in the treatment of this group. Expulsion rate of ureteral calculi <5mm is almost 85% without any therapeutic interventions. Therefore, choice of treatment

is just observation in this group.[3] The are many factors which many influence spontaneous expulsion of ureteral calculi such as stone site, dimension, count, and architecture; ureteral anatomy; inflammation in ureteric mucosa; and ureteric muscular spasm.[4]

Observation without surgical intervention may lead to many complications such as renal colic, hydronephroureter, acute pyelonephritis and sepsis.[5] To thwart such hazards and quicken spontaneous expulsion, numerous drug treatment have been used. These comprise calcium channel blockers, alpha1 receptor blockers, drugs that inhibit prostaglandins synthesis, steroids, and nitrates.[6] Physiologically, common site for alpha-1A and D adrenergic receptor subtypes are bladder neck, trigone, posterior part of urethra, and one-third distal end of the ureters. These receptors cause smooth muscle contractions at their sites. The most important blockage of spontaneous expulsion is at the intramural ureter, called the "detrusor tunnel."[7] Efficacy of alpha1-adrenergic receptor blockers in the treatment of distal ureteral stones have been studied in many researches. As Alpha blockers are able to decrease the spasm of ureteral smooth muscles, spontaneous passage of the stones was greater.[8]

Similarly, a competitive muscarinic antagonist, inhibits the phasic and tonic contractile activity induced by a submaximal concentration of carbachol in the porcine intra-vesical ureter and facilitate the intramural ureteric stone passage.[9]

In this trail, we evaluated the clinical outcome after giving alpha blocker i.e. Tamsulosin and an anticholinergic agent i.e. Tolterodine, used to lessen the resistance in the detrusor tunnel for expulsion of intramural ureteric stone.

Methodology

Total 104 subjects (90 men & 14 women) with distal ureteric calculi were included in this study during 6 months period from October 2017 to March 2018, which was conducted in Federal Government Polyclinic Hospital (polyclinic hospital), PGMI, Islamabad. Age of the patients ranged between 19 to 59 years with mean age of 31.5 years. Written informed consent was taken from the patients after local ethical committee approval. Individuals were included in the study who had ureteric calculi less than 10mm and had continence. On first visit complete blood count, serum electrolytes, and renal function test were performed. The patients underwent urine routine examination, X-ray KUB, ultrasound KUB and Non-contrast CT Scan if necessary. X-ray IVU (Intravenous urography) was done in selected candidates. After randomization with lottery method in 2 groups and patients were given respective drugs. Group 1 patients received Tamsulosin 0.4 mg/day, group 2 patients received Tamsulosin 0.4 mg/day plus Tolterodine 2 mg (twice a day), In addition, all patients were treated with prophylactic antibiotic therapy according to their culture and sensitivity along with adequate hydration daily. Diclofenac sodium 50mg twice daily will be given for first 7days only then after on patient need. Medical treatment was given for maximum period of 4 weeks. After first visit patients follow up was carried out 2 weekly. Ultrasound KUB (kidney, Ureters, Bladder), urine routine examination, renal function tests, and X-ray KUB were performed on follow up visits. During the treatment period the patient who had severe renal colic, those who developed urosepsis, or whose serum creatinine level was higher than 2 mg/dL were omitted from the study. Patients who didn't pass stone spontaneously by the end of the study underwent ureterorenscopy and lithoclasty or extracorporeal shockwave lithotripsy.

Those with stones less than 10 mm and allowing urinary flow were included in the study. Asymptomatic or incidentally found Intramural Ureteric Stone, Ureteric stone along with kidney stone, Presence of urinary sepsis, Chronic kidney disease stage 4 or stage 5, Pregnancy, Patients currently taking an α-blocker/Antimuscrinic agents, Gross hydronephrosis, Diabetes were excluded from the study.

All statistics entered and evaluated using SPSS version 21.0 For continuous variables like age and stone size, mean +_SD was calculated. To compare number of days of stone expulsion between both groups Independent sample t-test was used. To compare the efficacy between the two groups, Chi square test was used.

Results

One patient from group 1 and two patients from groups 2 were excluded from the study, and underwent Ureterorenoscopy to remove the stone because they developed severe renal colic and/or hydronephroureter, accompanied by high grade fever. No patient had to withdraw from the study because of any potential side effects secondary to medications.

Out of 52 patients in group 1, there were 44 (84.61%) male patients and 8 (15.38%) female patients (M:F; 5.5:1) and there were 46 (88.46%) male and 6 (11.53%)

females in group 2 (M:F;7.6:1). The average age of the patients in group 1 was 24.09±4.53 years and 28.58±7.46 years in group 2 respectively. The overall mean size of the intramural ureteric stone was 7.01±3.01mm. In both groups, right ureteric stones are more common than the left ureteric stones i.e. 78.84% and 69.23% respectively. The mean days of stone expulsion was 20.05± 6.11 and 10.41±4.63 days in group 1 and 2, respectively which was significantly shorter in group 2 (p-value, <0.001). Overall in 43 (82.6%) patients in group 2 and 34 (65.3%) cases in group 2, stone was expulsed before 28 days and, hence, combination therapy was found significantly better in ureteric stone expulsion compared to Tamsulosin alone. (Table I)

Table I: Statistical analysis of both groups

Gender	**Group 1 (n=52)**		**Group 2 (n=52)**	
	(n)	**(%)**	**(n)**	**(%)**
Male	44	84.61	46	88.46
Female	8	15.38	6	11.53
Age group(in years)				
18-20	6	11.53	4	7.69
21-30	26	50	21	40.38
31-40	12	23.07	18	34.61
41-50	7	13.46	6	11.53
51-60	1	1.92	3	5.76
61-65	0	0	0	0
Mean ± SD	24.09± 4.53 years		28.58±7.46 years	
Overall Mean ± SD	26.18±5.49 years			
Stone size(in mm)				
5-6	16	30.76	18	34.61
7-8	28	53.84	23	44.23
9-10	8	15.38	11	21.15
Mean ± SD	7.43± 2.11 mm		6.82±1.91 mm	
Overall Mean ± SD	7.01±3.01 mm			
Site of calculus				
Right ureter	41	78.84	36	69.23
Left ureter	11	21.15	16	30.76
Days of stone expulsion				
<28 days	34	65.3	43	82.6
>28 days	18	34.7	9	17.4
P Value <0.04				
Mean Stone expulsion duration (Days)				
Mean ± SD	20.05± 6.11		10.41± 4.63	
P Value <0.001				

Discussion

Early-stage permanent apoptotic modifications in the renal tubular cells occur swiftly and need complete stone clearance, even in the incomplete blockage of the ureter. Considering ureteric calculi of all sizes, the spontaneous clearance rate is highest when the stone size < 4 mm, but for stones greater than 6 mm clearance rate is<5%. However, for distal ureteral stones the spontaneous passage rate is about 50% using conservative treatment.[10] Many drug therapies have been proposed to increase the spontaneous clearance of stones.

In a randomized prospective study to evaluate the potential role of joint Tamsulosin and Tolterodine treatment for the spontaneous clearance of intramural ureteric calculi, the mean expulsion time for groups 1 and 2 was 7.62 ± 2.42, and 7.79 ± 2.11 days, respectively (P = 0.000). The rates of stone expulsion were 81.1% and 85.29% in group 1 and 2, respectively. It was concluded that therapy with Tamsulosin and Tolterodine combined was advantageous in intramural ureteral stone clearance.[11]

In another study by Lv JL et al, efficacy of Tolterodine (2 mg twice a day) for medical treatment of intramural ureteral stone was assessed with control group (watchful waiting) and the stone expulsion rate in control group and patients treated with Tolterodine, was 56.1% and 56.4%, respectively (P = 0.98). This study demonstrated that no improvement in rate of expulsion of stone was observed in patients who received Tolterodine.[12]

A randomized controlled trial done by Abdullah AA et al showed that the median time for spontaneous passage of calculus was 7 days in the Tamsulosin group compared with 10 days in the placebo group (log-rank test, p=0.36).[13]

Another randomized control trial by Ahmed H et al showed that patients administered Tamsulosin 0.4mg had stone passage rate of 85.71% (42 patients) compared to 54.20% (26 patients) in placebo group.[14]

Showed in a study by Dellabella M et al found that the Mean expulsion time was 65.7 hours for Tamsulosin and 111.1 hours for control group (p=0.020).[15]

Compared stone expulsion rate of Tamsulosin with Nifedipine and phloroglucinol. It was found to be 97.1% in Tamsulosin group, 77.1% in Nifedipine group and 64.3% in phloroglucinol group respectively. Another finding of this study was that Tamsulosin was associated with shorter stone expulsion time and with lesser hospitalizations, pain episodes and need for endoscopic procedures. Based on the observations researchers advocate the use of Tamsulosin as a first line agent in treatment of distal ureteric calculi.[15]

Mohammed AB et al discovered in their study that the mean time to spontaneous passage of stone was 7.32±0.78 days for Tamsulosin group (p=0.04) and 12.53±2.12 days for control group.[16]

There were many advantages of the current study, firstly; this was one of the very few studies on the management of ureteric stones in the local and national level settings. Secondly, a reasonable sample of 52 patients in each intervention arm was selected and followed up. A detailed view of efficacy of the two therapeutic arms was assessed.

The limitations were mainly related to the time span for study period, a limited period of 6 months was allocated for completion of the study.

Conclusion

In the present study, the expulsion of intramural ureteric stones were more observed in patients treated with combination therapy (group 2) than tamulosin alone therapy. The mean duration of expulsion of stones was also found significantly shorter in the combination therapy group. It is concluded that Tamsulosin combined with Tolterodine has a better effect in terms of intramural ureteric stone expulsion.

However, for generalization of the current study findings, further large scale trials on this topic with rigorous research methods are required in different healthcare and geographic settings nationally and internationally.

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