

To study and evaluate the efficacy of alpha 1 a-d receptors antagonist tamsulosin

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Abstract

Introduction: Effectiveness of tamsulosin in distal urolithiasis, which provide drastically comfort to the patient, considering stone expulsion, renal colic, expulsion time and costs.

Aim: To evaluate efficacy of tamsulosin in the expulsion of distal ureteral stones and to determine expulsion rate and time.

Materials and Methods: An interventional study was conducted in the department of surgery, Santosh Medical College and Hospital, Ghaziabad. 100 patients were included in study from 15–45 years of age and both sexes having a single unilateral stone of 2–8 mm size. Patients having multiple or bilateral stones, renal insufficiency, UTI, urinary retention, malignancy, history of previous surgery, hypersensitivity, taking calcium-antagonist or corticosteroid, renal abnormalities, were excluded from the study.

Results: The results showed an important role of tamsulosin for conservative expulsion of distal ureteric stones up to 8mm. There was no statistical significant difference in age and calculus size in the 61 males and 39 females. Ureteric calculi were more common on left side (56 patients) than right side (44 patients). Symptoms included flank pain in 100% of patients, dysuria in 17, vomiting in 10, haematuria in 6 patients. The diagnosis was confirmed by USG-KUB, X-Ray KUB or both. IVP helped in 1 case. 82% expulsion rate with tamsulosin, mostly within 1 week and with 1 mean colic episode was observed, better for smaller and left sided stones

Conclusion: Medical expulsive therapy with tamsulosin should be considered between conservative and surgical management.

Keywords: Ureteric colic, Lower end ureter, Alpha 1 a-d receptors, Tamsulosin.

Introduction

Urinary stones have plagued mankind since ages, earliest recorded being bladder stones detected in Egyptian mummies dated to 4800 B.C. Urolithiasis was a major health problem in 12 century BC when Susruta performed perineal lithotomy.¹ The etiology of stones remained obscure. Studies in last two centuries have resulted in the identification of composition of urinary stones.

Males more commonly afflicted than females (Male: female = 3:1). Due to testosterone levels in men, which caused increased endogenous oxalate production by the liver whereas in females increased urinary citrate concentrations has a protective effect.^{2,3}

Stones form in pelvicalyceal system when small they drop into the ureter and increase in size as they remain in the urinary passage. Small stones 5 mm pass spontaneously,^{4,5} some stones get arrested in the ureter producing complications such as obstruction, colic, infection, haematuria and acute renal failure. Such patients seek urgent relief.

The treatment of ureteral stones has undergone a remarkable evolution in the last 15yrs. Open ureterolithotomy and blind stone basket manipulation have been superseded by superior modalities like Ureteroscopy (URS) and Extracorporeal shock wave lithotripsy (ESWL).^{5,6}

Medical expulsive therapy (MET) has recently emerged as an alternative strategy for the initial management of small distal ureteral stones. The specific mechanism of action on the ureteral smooth muscle and low-risk profile suggest that alpha-adrenergic receptor antagonists (alpha-blockers) & calcium channel antagonists should be the initial medical treatment in patients amenable to conservative therapy.

Corticosteroids provide a small additive effect when combined with either alpha-blockers or nifedipine.

Recent studies have shown benefit to both α -blockers and calcium channel blockers without the adjunctive use of steroids; furthermore, tamsulosin, in a randomized trial, has been shown to be more efficient than nifedipine with a decreased time to expulsion and slightly higher rate of expulsion.⁷⁻¹¹

The highest incidence of calculi occurs between the ages of 20 and 40 years with male: female ratio being 3:1. The severity of the condition can be judged from the fact that about 10 percent of the patients harbouring a stone in the urinary system lose their kidney either by nephrectomy or as a result of subsequent destruction. The damaging effects of the calculi may result in obstruction with dilatation of the Urinary tract, leading to stasis and severe infection, with resultant fibrosis.

Ureter is the passage and the ureteric stone is just a passenger on its way from, the kidney, the site of its formation, to the urinary bladder. Many times these stones may recur. Frere Jacques, the famous lithotomist, of middle-ages has rightly exclaimed that “I have removed the stone but God will cure the patient.”¹²

The treatment that can be offered to the patient depends on many factors such as the size of the stone, obstruction or infection and site of impaction. The significance of proving the effectiveness of tamsulosin as a first-line therapy in distal urolithiasis therapy has the potential to drastically improve overall patient comfort by increasing stone expulsion, decrease the episodes of renal colic, time to expulsion, and reducing patient cost.

Aim

To assess and evaluate the efficacy of the alpha 1a-d receptor antagonist tamsulosin based on 6 weeks criteria in the expulsion of distal ureteral stones, with focus on (a) Rate of stone expulsion, and (b) Time to stone expulsion.

Materials and Methods

An interventional study was conducted in the department of surgery, Santosh Medical College and Hospital, Ghaziabad. Duration of study was from January 2017 to January 2018. 100 patients were included in study from 15–45 years of age and both sexes having a single unilateral stone of 2 – 8 mm size (at the level of S₂-S₃ sacral segment to the level of ischial spine which roughly corresponds to the vesico-ureteric junction). Patients having multiple stones in ureter or bilateral ureteric stones, renal insufficiency, urinary tract infection, urinary retention, a solitary kidney, bladder malignancy, any history of previous ureteral surgery or previous endoscopic procedure, hypersensitivity to tamsulosin, taking alpha-blocker, calcium-antagonist or corticosteroid medication, congenital renal abnormalities like duplication of ureter, stricture or stenosis of ureter or ureter with ectopic orifice were excluded from the study. Ethical clearance was obtained from Institutional Ethical Committee.

Alpha-1-adrenergic receptor antagonists have some degree of selectivity for the detrusor and the distal ureter and have therefore been the next agents investigated for their potential to promote stone expulsion and to decrease the pain.^{13,14} The likely mechanism of α -blockers use in stone passage has been to reduce ureteral spasm, increase pressure proximal to the stone, and relax the ureter in the region of and distal to the stone.¹⁵ The rationale in using α 1 antagonists has been that they are capable of decreasing the force of ureteral contraction, decreasing the frequency of peristaltic contractions, and increasing the fluid bolus volume transported down the ureter.¹⁶⁻¹⁸ Tamsulosin has been the most commonly studied α 1-blocker in the treatment of human prostate and ureteral stones; however, the data have been extrapolated and clinically tested on other α -blockers as well. At least three discrete alpha-1-adrenoceptor subtypes have been identified as: alpha1a, alpha1b and alpha1d; their distribution differs between human organs and tissue. Tamsulosin has equal affinity for α 1a and α 1d receptors.¹⁹ The α 1d receptor is the most common receptor in the ureter and is most concentrated in the distal ureter.²⁰ This study specifically addressed the

distal ureteric calculi of size < 8 mm presenting in emergency or OPD diagnosed clinically and confirmed radiologically by plain X-ray KUB (kidney, ureter and bladder), Ultrasonography KUB. The patients enrolled, underwent blood urea, serum creatinine and urine examination (Routine and microscopy), Urine (Culture and sensitivity), IVP (Intravenous Pyelography) and helical-NCCT (Non Contrast Computed Tomography) were performed as and when required.

The main endpoint in this study: stone expulsion with a time frame of six weeks and the patients were followed at 1 week, 3 weeks, 6 weeks and when required. An X-Ray KUB (Kidney, Ureter and Bladder), ultrasonography KUB were done and followed up at one week, 3 week and 6 weeks. Other clinically significant secondary endpoints included: time to expulsion, pain, and medication side effects, which further illustrated the effectiveness of tamsulosin administration in the presence of distal urolithiasis. The ultimate goal and purpose of this study was to continue further the evaluation of medical expulsion therapy (MET) as a first-line urolithiasis treatment modality by assessing the use of tamsulosin in the presences of distal ureteral stones in the adult population. The medication's mechanism of action, blockage of the alpha-receptor 1a-d, theoretically makes tamsulosin an excellent choice when considering the abundance of alpha 1-receptor sites in the distal ureter. By the evaluation of the main endpoint: stone expulsion and secondary endpoints including: time to stone expulsion, medication side effects, and evaluation of pain.

If the patient situation worsened symptomatically i.e. persistent rise of temperature, frequent episodes of ureteric colic, worsening hydro-ureteronephrosis, the study of concerned was abandoned and there by advanced to the minimal invasive urological instrumentation was considered.

Data that collected through all these tools were entered in MS-EXCEL and the variables identified were analyzed. Statistical analysis was done using the statistical package for the social science system (SPSS) version 17.0. Continuous variables are presented as mean \pm SD and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. P<0.05 was considered statistically significant.

Table 1: Age wise and gender wise distribution of cases

S. No.	Age group	Female	Male	Total
01	15 - 25	18	19	37
02	26 – 35	09	21	30
03	36 - 45	12	21	33
Total		39	61	100

Table 2: Showing distribution of samples by symptoms and investigations

Symptoms	Symptoms		No.	Percentage
		Flank Pain		68
	Flank Pain + Dysuria		16	16%
	Flank Pain + Vomiting		10	10%
	Flank Pain + Haematuria		05	05%
	Flank Pain + Dysuria + Haematuria		01	01%
	Total		100	100%
Detected by	USG-KUB		59	59%
	X-Ray KUB		27	27%
	USG-KUB + X-Ray KUB		13	13%
	IVP		1	1%
	Urine-Routine	RBC		51
Pus Cells			37	
Casts			14	

Table 3: Gender wise distribution, rate and frequency of expulsion of stone, colic episodes and success rate in group 1 and group 2

S. No.	Stone Size	Gender		Total No. of Cases	No. of cases with expulsion of stone	Mean number of days	Total number of patients who expelled the stone	Total number of colic episodes	Mean number of colic episodes	Success (%)
		Male	Female							
01	Group 1 (≤5mm)	17	14	31	29	5.83	29	26	0.89	93.5
02	Group 2 (6-8mm)	44	25	69	53	7.19	53	63	1.19	76.8
Total		100		100	82	6.79	82	89	1.09	82
		p value >0.05			P value < 0.05	P value >0.05	p value >0.05			

Table 4: Distribution by laterality, gender, mean size and expulsion

S. No.	Laterality	Total No. of Cases		Mean size(mm)		No. of cases with expulsion of stone		Total Expulsion	Success (%)
		Male	Female	Male	Female	Male	Female		
01	Left U.S.	56	P value	6.12 mm	P value	25	24	49	87.5
02	Right U.S.	44	<0.05	6.20 mm	>0.05	22	11	33	75
Total				100		47	35	82	82

Table 5: Expulsion of stone time in weeks

S. No.	No. of weeks	Total Cases who expelled the stone (N=82)	Percentages (%)
01	Ist	56	68.3
02	IInd	24	29.3
03	IIIrd	02	2.4
Total		82	100.0

P = <0.05 (Significant)

Results

The results showed an important role of tamsulosin for conservative expulsion of distal ureteric stones upto 8mm. There was no statistical significant difference in age and calculus size in the 61 males and 39 females. Ureteric calculi were more common on left side (56 patients) than right side (44 patients). Symptoms included flank pain in 100% of patients, dysuria in 17, vomiting in 10, haematuria in 6 patients. The diagnosis was confirmed by USG-KUB, X-Ray KUB or both. IVP helped in 1 case. 82% expulsion rate with tamsulosin, a surgical intervention rate as low as 11%, mostly within 1 week and with 1 mean colic episode was observed, better for smaller and left sided stones.

Discussion

In present study in the group I 31 (31%) patients had stone size <5mm whereas in the group II 69 (69%) patients had stone size 6-8 mm. In left side USG mean stone size is 6.12 mm and in Right side USG it is 6.20 mm and the difference was observed to be statistically insignificant. Dellabella M. et al. in their study observed that mean stone size in two groups was 5.8 and 6.7 mm ($p=0.001$).²¹ Ahmed H. et al. reported mean stone size to be 5.78mm (range 4-8mm) in greatest dimension.²² Sebastein V. et al. studied that out of total 129 patients, at inclusion, mean (SD) stone diameters were 3.2 (1.2) and 2.9 (1.0) mm in the placebo and tamsulosin groups.²³ In present study in group A only 26 (83.87%) patients experienced colics whereas in group B 63 (91.3%) patients reported colics with no statistical significance as p value was >0.05. Resim S. et al. observed that as group 1 patients were passing their stones, they had more ureteral colic episodes than group 2 patients.²⁴ This difference was statistically significant and correlated well with the administration of tamsulosin ($P=0.038$). Mohammed A.B. et al. in their study found that the number of pain episodes was significantly lower in patients of group B (tamsulosin group) and mean use of analgesics was lower for group B (0.14 ± 0.5 vials) than group A (2.78 ± 2.7 vials).²⁵ M S Griwan et al. observed that group II (tamsulosin group) showed a statistically significant advantage in terms of mean number of pain episodes.²⁶ In present study mean time of stone expulsion for group I and II were 5.83 and 7.19 days respectively with insignificant difference ($p>0.05$) in both groups. Abdullah A.A. et al. in their double blind randomized controlled trial observed that Median time to stone passage was 7 days in the tamsulosin arm and 10 days in the placebo arm (log-rank test, $p=0.36$).²⁷ The difference between number of cases of stone expulsion between both groups was found to be statistically significant ($p<0.05$) as in group I patients, who were given capsule tamsulosin 0.4mg had stone expulsion rate of 93.54% (29 patients) and 76.81% (53 patients) in group II patients. Ahmed H et al observed in a randomized control trial that group A patients, who were given capsule tamsulosin 0.4mg had stone expulsion rate of 85.71% (42 patients) and 54.20% (26 patients) in group B patients (placebo group).²² Considering expulsion time in days no statistically significant advantage ($p>0.05$) was found. Ferre

M.R. et al. found in their study that successful spontaneous stone expulsion at 14 days was similar between the groups, with 27 (77.1%) subjects in the tamsulosin group and 24 (64.9%) subjects in the standard therapy group, a difference of 12% (95% CI- 8.4% to 32.8).²⁸ Dellabella M. et. al. observed in their study that Mean expulsion time was 111.1 hours for control group and 65.7 hours for tamsulosin group ($p=0.020$).²¹ Mohammed A.B. et. al. found in their study that the average time to expulsion was 12.53 ± 2.12 days for group A (control group) and 7.32 ± 0.78 days for group B (tamsulosin group) ($p=0.04$).²⁵ In present study in group I 29 out of 31 patients (93.54%) successfully expelled stone who had stone size of <5mm whereas in group II this proportion was 53 out of 69 (76.8%). Overall expulsion rate in group I was 93.5% whereas in group II it was only 76.8%. Mohammed A.B. et al. found in their study that the stone expulsion rate was 51.1% for group A (regular), compared to 88.9% for group B (Tamsulosin) ($p=0.001$).²⁵ The proportion of cases and controls when analysed for size of stone expelled were observed to be statistically highly significant ($\chi^2=11.67$, $df=1$, $p=0.001$). Abdullah A.A. et al. observed in their double blind randomized controlled trial that no statistically significant differences in patient characteristics and stone size (median: 4.1 mm [tamsulosin arm] vs 3.8 mm [placebo arm], $p = 0.3$) were found between the two treatment arms.²⁷ The stone expulsion rate was not significantly different between the tamsulosin arm (86.7%) and the placebo arm (88.9%; $p=1.0$). Gupta G et. al. observed stone free rate were higher in tamsulosin group and less number of times use of diclofenac as well as less time to expulsion of fragments were prominent findings of study.²⁹ In present study stone expulsion was found to be the maximum in the first week (68.3%), followed by II week (29.3%) and least being in the third week (2.4%) with a statistical significant difference found ($p<0.05$). Our findings are quite similar to that of Chandawat P.S. et al. concluded that tamsulosin should be considered for uncomplicated distal ureteral calculi before ureteroscopy or extracorporeal lithotripsy. Tamsulosin has been found to increase and hasten stone expulsion rates, decrease acute attacks by acting as a spasmolytic, reduces mean days to stone expulsion and decreases analgesic dose usage.³⁰

Conclusion

The results of this study have shown a potentially important role of tamsulosin for conservative expulsive therapy of distal ureteric stones of size upto 8mm. To validate these promising and statistically significant results, further study with larger sample size is necessary taking into consideration a predominant role of first line pharmacological treatment easily providable on outpatient basis. Also, tamsulosin proved to be much more efficient in expulsion of ureteric stones in less time and proved to be safe and effective on the basis of the increased stone expulsion rate and reduced expulsion time. In conclusion, medical expulsive therapy with tamsulosin is an effective bridge between watch-and-wait management and surgical intervention.

Conflict of Interest: None.

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