



DOES PREOPERATIVE ALPHA BLOCKER ACTUALLY HELPS IN NEGOTIATION OF 8/9.8 FR URETEROSCOPE THROUGH VESICoureTERIC JUNCTION? A SINGLE CENTER RANDOMIZED TRIAL.

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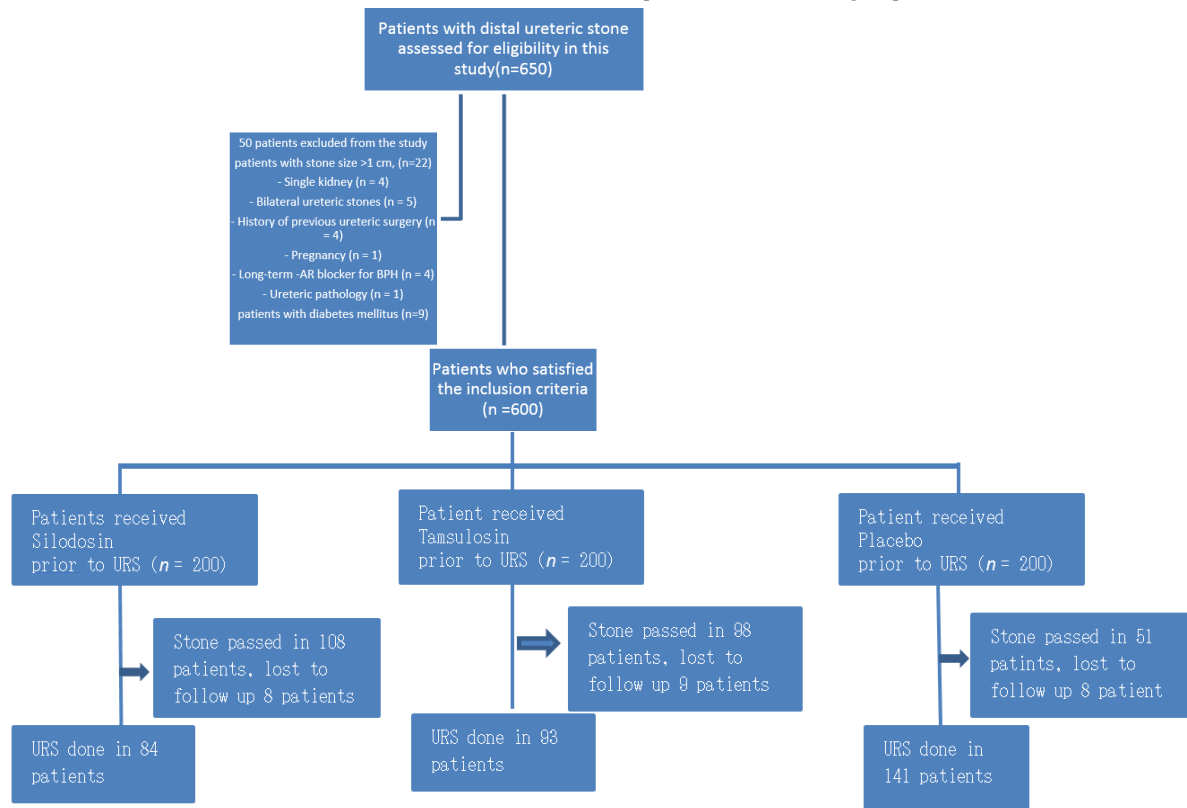
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INTRODUCTION

Urolithiasis is a global public health problem. The prevalence rates which were estimated, fluctuates ranging from 7–13% in North America, 5–9% in Europe, and 1–5% in Asia.¹ Renal colic due to ureteric calculus is one of the leading cause for frequent visits to hospital emergency departments. About 70% of the ureteral stones were located in lower third of the ureter.² As per the European Association of Urology (EAU) (2020), medical expulsive therapy (MET) is recommended for treating patients with ureteral stones and utmost benefit is seen among those having >5mm distal ureteral stones. Alpha blockers, mainly tamsulosin, have shown efficacy to aid stone passage in several randomized controlled trials.^{3,5} Mechanism of action of alpha blockers in distal ureter is via alpha adrenergic receptors (alpha-1D and alpha-1A), which are abundant in distal ureter.⁶ Blocking the action of alpha-1 receptors by alpha blockers such as Alfuzosin, Silodosin and Tamsulosin results in the relaxation of the ureteric smooth muscle.⁷⁻⁹

The most commonly performed treatment procedure for ureteral calculi is ureterscopic stone removal, having >90% stone-free rate after single procedure. Usually, before ureteroscopy with semi rigid ureteroscope 8/9.8 Fr size, dilation of ureteric orifice is essential either with active or passive dilation which increases the operative time and cost of the procedure. With miniaturisation and technical advancements in the design of semi-rigid ureteroscope, prior dilation is not required but it has limitations of small field of vision, small working channel for instrumentation and delicacy of the instrument. The role of alpha-blockers has been well established in MET of ureteric calculus. We have observed the cases where patient underwent URS after failed MET for 10 days and found patulous ureteric orifice facilitating easy negotiation at ureteric orifice. The present prospective, case-controlled study has been done to compare ease of negotiation of ureteroscope at vesicoureteric junction (VUJ) in patients who had received preoperative alpha blockers (Tamsulosin or Silodosin) and no alpha blockers (control group).



Flow chart of study inclusion

MATERIAL AND METHODS**Study Design**

We conducted a prospective, case-controlled study of 650 patients at the Urology Department, Government medical college, Kota (Rajasthan), who underwent ureteroscopic stone removal for lower ureteric calculi between October 2017 and March 2020. Written informed consent was obtained from all recruited patients and performed according to the local ethics of our institute. We included patients >14 years of age who were diagnosed cases of lower ureteric calculus (6-10mm size). Patients were allocated to three groups randomly using a closed-envelopes method. Each group included 200 patients, first group received Silodosin (8 mg) for 10 days before URS (Silodosin group), second group received Tamsulosin (0.4mg) for 10 days before URS (Tamsulosin group) whilst the third group received placebo, in the form of multivitamins supplementation, for 10 days before URS (Placebo group).

We excluded patients with stone size >1 cm, patients with ureteral strictures and ureteral anomalies, prior history of URS or DJ stenting, reimplanted ureter, diabetes mellitus, bilateral ureteric stones, single kidney, prior long term alpha blocker use for the management of benign prostatic hyperplasia.

The data of all enrolled patients were collected in form of age, sex, BMI, occupation, medical history about stone related symptoms, previous treatment, urinalysis, urine culture, x-ray KUB (kidney, ureter, and bladder), ultrasound KUB, excretory urogram, or non-contrast computed tomography KUB (NCCT-KUB). All patients were treated preoperatively as per urine culture report. We calculated stone size by multiplying the two largest dimensions on available radiological study (x-ray KUB, ultrasound KUB, excretory urogram, or NCCT-KUB).

All patients were followed up on 10th day with ultrasound KUB and x-ray KUB. Patients who had passed stone with MET or with placebo were excluded from study. Rest of the patients were planned for URS. URS was done by experienced urologists who had done more than 100 URS in the past. Intraoperative and postoperative data, including procedure time and complications, were recorded (Table 1). All patients stopped taking Silodosin, Tamsulosin or placebo immediately postoperatively. Urologists who carried out the operations were blinded to all three groups.

Operative technique

After giving spinal anaesthesia, patients were placed in lithotomy position & cystourethroscopy was done to examine urethra and bladder, and ureteric orifice. A 0.089 cm (0.035 in.) terumo guidewire was placed via ureteric orifice under fluoroscopic guidance till it reaches the kidney. After which the ureteroscope (8/9.8 F, Richard Wolf) was hosted to the ureteric orifice. Wherever necessary, balloon dilatation was done to dilate the ureteric orifice for facilitating the entry of ureteroscope. On advancing, the ureteroscope into the ureter, the stone was accessed and fragmented using a pneumatic lithoclast. The fragments were removed with a biprong/ triprong forceps. At the end of procedure, a 5F ureteral DJ stent was inserted according to indication [13]. The patients were then evaluated for stone clearance at 24–48 hrs after the procedure using KUB and pelvi-abdominal US. All patients were asked to attend the clinic after 2 weeks to undergo follow-up assessment using KUB and pelvi-abdominal US. Patients were considered stone-free if there were either no residual stone fragments (<2mm) or no signs of hydronephrosis. Fever was considered present whenever the body temperature was more than 38C. Haematuria requiring i.v. fluids for >12 h was considered noteworthy. The data of all three groups, including need for dilatation of the ureteric orifice, results of advancing the ureteroscope to access the stones, complications, operative time and stone-free rate were noted and analyzed.

Statistical analysis of data was performed with the SPSS Windows version 11.0 by using Student's t-test and chi-square test. $p < 0.05$ was considered statistically significant.

RESULTS

The total number of patients analyzed were 84, 93 and 141 in the Silodosin group, Tamsulosin group and Placebo group, respectively (Table 1). The mean (SD) age of patients was 39.28 (8.25) years in the Silodosin group and 38.77(8.55) years in Tamsulosin group and 38.22(8.34) years in the Placebo group. In the Silodosin group, 63.09 % of patients were male and 36.91% were female, in the Tamsulosin group 58.06% were male and 41.94 % were female and in Placebo group, 60.99% were male and 39% were female.

There were no statistically significant differences among the groups for age and sex distribution of the patients. Also, there was no statistically significant difference among the groups for stone size, side, and density. The mean (SD) stone size was 8.77(.412) mm in the Silodosin group and 8.69(0.402) mm in Tamsulosin group and 8.53(0.490) mm in the Placebo group. There was no statistically significant difference among groups for the body mass index. Operative and postoperative data were presented in Table 2. The operative time was significantly shorter in the Silodosin group and Tamsulosin group than in the Placebo group, at a mean (SD) of 42.55(4.97)min, 43.28(5.12)min and 53.33(6.45)min respectively ($P < 0.001$). The need for ureteric orifice dilatation was significantly higher in the Placebo group compared with the Silodosin group and Tamsulosin group at 69.28 %, 16.66 % and 21.50% respectively ($P < 0.001$). The overall complications rate were significantly higher in the Placebo group compared with the Silodosin group and Tamsulosin group 32.62 %, 16.66 % and 17.20% respectively ($P = 0.036$). Fever occurred in 6 cases in the Silodosin group, 7 cases in Tamsulosin group and in 15 cases in the Placebo group. In all cases the fever abated within 48 hrs with antibiotic and antipyretic management (Clavien–Dindo Grade I). Hematuria occurred in 4 cases in the Silodosin Group, 5 cases in Tamsulosin and 16 cases in the Placebo group, which were treated by i.v. fluid continuation for 24–48 h (Clavien– Dindo Grade I). There was mucosal injury intraoperatively in 3 cases in the Silodosin group, 3 cases of Tamsulosin group and 12 cases in the Placebo group (Clavien–Dindo Grade I).

(Table 1). The patients' and stone characteristics are given-

Variables	GROUP 1 (Silodosin group)	GROUP 2 (Tamsulosin group)	GROUP 3 (Placebo group)	P Value		
				Gr1 /3	Gr 2/3	Gr 1/2
No. of patients	84	93	141			
Age, years, mean(SD)	39.28 ± 8.25	38.77 ± 8.55	38.22 ± 8.34	.81	.69	.72
Sex, n(%)						
Male	53(63.09)	54(58.06)	86(60.99)	.75	.65	.49
Female	31(36.91)	39(41.94)	55(39.00)	.83	.79	.74
Stone size, mm, mean (SD)	8.77 ± .412	8.69 ± 0.402	8.53 ± 0.490	.71	.77	.72
Stone side, n(%)						
Right	51(60.71)	57(61.29)	89(63.12)			
Left	33(39.29)	36(38.71)	52(36.87)			
BMI, kg/m ² , mean(SD)	27.75(2.22)	27.28(2.35)	27.46(2.29)	.88	.78	.83

Table 2 operative and postoperative data

Variable	Silodosi- ne group	Tamsulo- sin group	Control group	P value		
				Gr 1/3	Gr2/3	Gr1/2
Ureteric orifice dilatation (overall), n (%)	14(16.66)	20(21.50)	97(69.2 8)	<.001	<.00 1	0.637
Operative time, min, mean (SD)	42.55±4. 97	43.28±5. 12	53.33± 6.45	0.004	0.005	0.745
Overall complicati- ons, n (%)	14(16.66)	16(17.20)	46(32.6 2)	0.908	0.867	0.996
Stone migration (Clavien- Dindo Grade IIIa)	1(1.19)	1(1.07)	3(2.12)			
Fever (Clavien- Dindo Grade I)	6(7.14)	7(7.52)	15(10.6 3)			
Mucosal injury (Clavien- Dindo Grade I)	3(3.57)	3(3.22)	12(8.51)			
Haematuria (Clavien- Dindo Grade I)	4(4.76)	5(5.37)	16(11.3 4)			
Stone-free rate, n/N (%)						
At 24–48 h	81/84(96. 42)	87/93(93. 54)	114/141 (80.85)	0.0183	0.003 2	0.508

DISCUSSION

In recent years, URS has become the gold standard treatment option for distal ureteric stones in patients who had failed MET.¹⁰ The present study is limited to distal ureteric stones, as we thought that the action of alpha blocker is maximum at distal ureter than proximal and middle ureter.¹¹ Mechanism of action of alpha blockers has been described over distal ureter is through alpha 1a- and alpha 1d-ARs.¹² As per Sasaki et al.¹³ the alpha 1a-AR subtype is responsible for the majority of the contraction process in the human ureter. Therefore, inhibition of these receptors should result in relaxation of ureteric smooth muscles and dilatation of the ureteric lumen.^{14,15} The benefit of alpha-AR blockers as medical expulsive therapy for ureteric stones is well established in the literature, and also in practice as they increase the stone passage rate and minimise expulsion time.^{16,17} Tamsulosin is an Alpha 1A/1D blocker and Silodosin is an Alpha 1A blocker.^{18,19} Both act on distal ureter and decrease peristaltic activity, contractile pressure and baseline pressure, so it would be easy to pass a semi-rigid ureteroscope.

In our center, we have both 8/9.8 fr and 6.4/7.8 fr semirigid ureteroscope and we found that in most cases of URS, we have to dilate the ureteric orifice to negotiate the 8/9.8 fr ureteroscope and it was not the case with 6.4/7.8 fr ureteroscope. Dilatation is an additional step which increases the procedure time and also increases the necessity of DJ stenting after procedure. We took an idea from medical expulsion therapy, where stone is expelled out due to dilatation effect on lower ureter and ureteric orifice by alfa blockers. We worked on this idea in MCh residency training and presented a poster in USICON 2014. But study was not published due to small sample size. The present study is

prospectively designed to assess the efficacy of preoperative Silodosin or Tamsulosin therapy on ease of negotiation of semi-rigid URS 8/9.8 fr for distal ureteric stones.

In the practice, the mean time for the distal ureteric stone passage with MET was 8.3days.²⁰ Therefore, patients received 10 days therapy before URS thus giving an adequate duration to relax the ureteric smooth muscles and facilitating negotiation of the ureteroscope. Ahmed et al.²¹ reported that the use of tamsulosin (an alpha-AR blocker) as adjunctive therapy prior to semi rigid URS for the management of proximal ureteric stones increased the success rate and minimized the rate of complications. Aydin et al.²² showed that administration of Silodosin before URS for managing stones located at all levels of the ureter achieved a higher access rate with lower complications. Ahmed et al.²¹ and Aydin et al.²² reported that access to the stone failed in 12.1% and 17% of cases, respectively.

In the present study, negotiation of ureteroscope through VUJ succeeded in 70/84 cases in the Silodosin group, 73/93 whilst in the Placebo group success was achieved in 44/141 cases. This supports the finding that blocking of α-ARs located in the distal ureter leads to ureteric smooth muscle relaxation and decreases the force and frequency of the peristalsis.^{6,11} There was a need for ureteric orifice dilatation in 14 patients (16.66%) in the Silodosin group, 20 patients (21.50%) in Tamsulosin group compared with 97 (69.28%) in the Placebo group (P < 0.001). We suspect this significant difference is related to the effect of Silodosin and Tamsulosin.

In the present study, the mean operative time was shorter in the Silodosin and Tamsulosin group than the Placebo group. This significant difference may be due to the time taken for ureteric orifice dilatation and for advancing the ureteroscope to access the stone, which was easier and faster in the Silodosin group and Tamsulosin group. This result is congruent with Ahmed et al.²¹, who reported that operative time was shorter in patients who received Tamsulosin. However, Aydin et al.²² did not find a significant difference in the operative time between the studied groups.

In the literature, the reported overall complication rates for URS range from 9% to 25%.^{23,25} In the present study, the overall complication rate was higher in the Placebo group than the Silodosin and Tamsulosin group (32.62% vs 16.66% vs 17.20%) respectively. We consider that the success of advancing the ureteroscope to access the stones with ease, swiftly and with less complication without dilatation was the cornerstone of the present study.

The fact that the procedures were performed by multiple surgeons could be considered a limitation of the present study. However, all the surgeons were consultants and had previously performed >100 semi-rigid URSs. We hope to see future randomized studies from other institutions for further confirmation of the efficacy of alpha blockers prior to URS for the management of large distal ureteric stones.

CONCLUSION

Alpha blockers are effective, economical and safe preoperatively for ureteroscopy with 8/9.8 fr ureteroscope without dilatation. Both drugs are almost equal in results.

REFERENCES

1. Ramello A et al. Epidemiology of nephrolithiasis. J Nephrol. 2000;13 Suppl 3:S45-50.
2. Zhang MY et al. Comparison of tamsulosin with extracorporeal shock wave lithotripsy in treating distal ureteral stones. Chinese Med J (Engl). 2009; 122(7):798-801.
3. Lee JK et al. Impact of tamsulosin on ureter stone expulsion in Korean patients: a meta-analysis of randomized controlled studies. Korean J Urol. 2012; 53(10):699-704.
4. Seitz C et al. Medical therapy to facilitate the passage of stones: what is the evidence? Eur Urol. 2009;56(3): 455-71.

5. Lu Z et al. Tamsulosin for ureteral stones: a systematic review and meta-analysis of a randomized controlled trial. *Urol Int*. 2012;89(1):107-15.
6. Sigala S et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. *Neurourol Urodyn*. 2005; 24(2):142-8.
7. Elliott HL et al. A pharmacodynamic and pharmacokinetic assessment of a new alpha-adrenoceptor antagonist, doxazosin (UK33274) in normotensive subjects. *Br J Clin Pharmacol*. 1982; 13(5):699-703.
8. Lefèvre-Borg F et al. Alfuzosin, a selective alpha 1-adrenoceptor antagonist in the lower urinary tract. *Br J Pharmacol*. 1993;109(4):1282-9.
9. Noble AJ et al. The effects of tamsulosin, a high affinity antagonist at functional alpha 1A-and alpha 1D-adrenoceptor subtypes. *Br J Pharmacol*. 1997;120(2):231-8.
10. Netto Ju'nior NR, Claro Jde A, Esteves SC, Andrade EF. Ureteroscopic stone removal in the distal ureter. Why change? *JUrol* 1997;157:2081-3.
11. Malin Jr JM, Deane RF, Boyarsky S. Characterisation of adrenergic receptors in human ureter. *Br J Urol* 1970;42:171-4.
12. Itoh Y, Kojima Y, Yasui T, Okada A, Tozawa K, Kohri K. Examination of alpha 1 adrenoceptor subtypes in the human ureter. *Int J Urol* 2007;14:749-53.
13. Sasaki S, Tomiyama Y, Kobayashi S, Kojima Y, Kubota Y, Kohri K. Characterization of a (1)-adrenoceptor subtypes mediating contraction in human isolated ureters. *Urology* 2011;77:e13-7.
14. Ueno A, Kawamura T, Ogawa A, Takayasu H. Relation of spontaneous passage of ureteral calculi to size. *Urology* 1977;10:544-6.
15. Porpiglia F, Vaccino D, Billia M, Renard J, Cracco C, Ghignone G, et al. Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? *Eur Urol* 2006;50:339-44.
16. Griwan MS, Singh SK, Paul H, Pawar DS, Verma M. The efficacy of tamsulosin in lower ureteral calculi. *Urol Ann* 2010;2:63-6.
17. Sayed MA, Abolyosr A, Abdalla MA, El-Azab AS. Efficacy of tamsulosin in medical expulsive therapy for distal ureteral calculi. *Scand J Urol Nephrol* 2008;42:59-62.
18. Martin DJ, Lluell P, Guillot E, Coste A, Jammes D, Angel I. Comparative alpha-1 adrenoceptor subtype selectivity and functionaluroselectivity of alpha-1 adrenoceptor antagonists. *J Pharmacol Exp Ther* 1997;282:228-35.
19. Tatemichi S, Kobayashi K, Maezawa A, Kobayashi M, Yamazaki Y, Shibata N. Alpha1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213). *Yakugaku Zasshi* 2006;126:209-16 [Article in Japanese].
20. Huang W, Xue P, Zong H, Zhang Y. Efficacy and safety of silodosin in the medical expulsion therapy for distal ureteral calculi: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2016;81:13-22.
21. Ahmed AF, Maarouf A, Shalaby E, Alshahrani S, El-Feky M, Khaled S, et al. Semi-rigid ureteroscopy for proximal ureteral stones: does adjunctive tamsulosin therapy increase the chance of success? *Urol Int* 2016;98:411-7.
22. Aydin M, Kilinc MF, Yavuz A, Bayar G. Do alpha-1 antagonist medications affect the success of semi-rigid ureteroscopy? A prospective, randomised, single-blind, multicentric study. *Urolithiasis* 2017. <https://doi.org/10.1007/s00240-017-1026-6> [Epub ahead of print].
23. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck C, Gallucci M, et al. 2007 guideline for the management of ureteral calculi. *J Urol* 2007;178:2418-34.
24. Geavlete P, Georgescu D, Nit, a G, Mirciulescu V, Cauni V. Complications of 2735 retrograde semirigid ureteroscopy procedures: a single center experience. *J Endourol* 2006;20:179-85.
25. Perez Castro E, Ooster PJ, Jinga V, Razvi H, Stravodimos KG, Parikh K, et al. Differences in ureteroscopic stone treatment and outcomes for distal, mid-, proximal, or multiple ureteral locations: the Clinical Research Office of the Endourological Society ureteroscopy global study. *Eur Urol* 2014;66:102-9.