

# Tamsulosin as a Medical Expulsive Therapy for Distal Ureteric Stones: A Prospective Matched-Control Study With Different Stone Settings

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## Abstract

**Introduction:** We aimed in our study to study the role of tamsulosin in stone clearance with different distal ureteric stone settings.

**Material & Methods:** A prospective study between January 2015 and December 2016, the study included all patients who took tamsulosin and divided into 2 different groups; de novo stones less than 6 mm (Group 1) and stones 6-12 mm as adjunctive therapy to ESWL (Group 2). Patients were compared to matched groups through 2013 and 2014 who didn't take the medication. Either IVU or CT was performed for all patients. The primary outcome was passage of the stone. A second ESWL session was considered after three weeks for no clearance, and URS was considered if no clearance after three weeks from the 2nd ESWL session.

**Results:** A total of 163 patients were included in the study. Overall, tamsulosin decreased the frequency of renal colic, parental analgesia and hospitalization in all groups, but had no benefit on stones less than 6 mm. In Groups II, tamsulosin showed better results in stone clearance, the necessity to ESWL and URS which sustained their significance in multivariate analysis in comparison to the control groups ( $p < 0.05$ ). A total of 14 (7%) events were recorded with side effects; retrograde ejaculation, dizziness, and headache were the most common.

**Conclusion:** Tamsulosin showed the maximum benefit as an adjunctive therapy to ESWL for 6-12 mm stones, and no benefit on stones less than 6 mm in comparison to control groups.

**Keywords:** Urinary tract calculi; Ureteric calculi; Distal ureteric stones; Medical expulsive therapy; Tamsulosin; Adrenergic  $\alpha$ -blockers

## Introduction

Urinary tract stone disease is a common health problem affecting 8-15% of the population and the prevalence, and incidence of nephrolithiasis is reported to be increasing across the world [1]. Ureteral stones comprise 20-30 % of all urinary tract calculi and 70% of them in the lower ureter [2]. Extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) are known as effective methods for treatment of ureteric stones [3,4]. Medical expulsive therapy (MET) is another non-invasive treatment that aims for spontaneous passage of stones through the ureter [5,6].

Alpha blockers agents, like alfuzosin [7] and silodosin [8], were tried for this purpose. Tamsulosin is a selective  $\alpha$  1a receptor blocker that has been approved for BPH. However, its role in the

clearance of ureteric stones is still controversial. Many trials have proven its effectiveness as adjunctive therapy to ESWL [9-11] and in the passage of the stones in steinstrasse setting [12,13]. On the other hand, many prospective randomized trials have not shown its superiority over placebo [6,14,15].

We aimed to further study its role in different stone settings (de novo ureteric stones and adjunctive therapy to ESWL) to determine its role in the clearance of the stones, and decreasing the need for further ESWL, and URS sessions.

## Subjects and Methods

After institutional board approval (676/2015), a prospective study was conducted between January 2015 and December 2016. A valid informed consent was obtained from all patients and the contribution was completely voluntary.

**Study population:** All patients who had lower (below the pelvic brim) ureteric stones were identified and classified into 2 groups; stones less than 6 mm and stones 6-12 mm as adjunctive therapy to ESWL following ESWL.

**Elimination Criteria:** The followings were eliminated from the study; pediatrics, pregnant women, gross hydronephrosis, any urosepsis, and lower ureteric abnormalities (ureterovesical reflux, mega ureter or lower ureteric stricture). Also, patients with history of URS or surgical procedures on the lower ureter were eliminated.

**Preoperative workup:** Physical exam, routine laboratories like urine analysis, urine culture, blood sugar, blood creatinine; Ca and uric acid, Routine imaging like X-ray (kidney, ureter and bladder film) and US were done for all patients. Either computed tomography (CT) or intravenous urography (IVU) was done for all patients.

**Intervention:** All patients were advised to drink plenty of fluids (4L/day), and were given analgesia (diclofenac tab/Injection when indicated). All patients with urine culture were treated with appropriate antibiotics, and tamsulosin 0.4 mg tab was given daily to all patients.

**Control:** Patient who had lower ureteric stones between January 2013 and December 2014 were used who didn't use tamsulosin as control groups. Also, they were identified and classified into 2 groups; stones less than 6 mm and stones 6-12 mm as adjunctive therapy to ESWL. Matching with the study groups was put in consideration to fulfil as matched-control arm.

**Outcomes:** The primary outcome was passage of the stone. Others include the necessity to ESWL or URS, parenteral analgesia usage and episodes of renal colic.

**Follow up:** Patients were asked to attend weekly, and were given a simple questionnaire that inquired about the stone clearance and the other outcome. A second ESWL session was considered after 3 weeks for no clearance and URS was considered if no clearance after three weeks from the 2nd ESWL session.

**Statistical analysis:** Data were collected in a Microsoft Excel spreadsheet. After coding, the data were transferred to SPSS, version 16 for further analysis. Non-continuous data were reported as frequencies and percentages and chi square test was used for analysis. For numeric data with normal distribution, the mean + standard deviation was used for expression and t-test was used for analysis; otherwise, the median and range were used and Mann-Whitney U test for analysis. Binary logistic regression analysis in a forwards LR- selection strategy was used. In all tests, the p- value was 2-sided, and significance was set at  $p < 0.05$ .

## Results

Of 224 patients who were enrolled in the study, 163

patients were found with completed files, and were included in the study. The mean age was  $36 + 7$ , and 65 % were male. Group I (72 patients) took tamsulosin for distal ureteric stones less than 6 mm and group II (91 patients) as adjunctive therapy to ESWL for stones 6-12 mm.

For group I, tamsulosin showed a higher stone expulsion rate within 4 weeks, and decreased the need for ESWL and URS (Table 1) in comparison to the control group. However, they did not sustain their significance in multivariate analysis, but the frequency of renal colic episodes, necessity of parental analgesia and hospitalization did ( $p < 0.05$ ).

For group II, tamsulosin showed better results in clearance, the necessity to ESWL and URS (Table 2) in comparison to the control group. They sustained their significance in multivariate analysis ( $p < 0.05$ ) (Table 2b). Also, fewer episodes of renal colic and parental analgesia.

Tamsulosin was well tolerated, and few side effects were noted. A total of 14 events were recorded, retrograde ejaculation, dizziness, and headache were the most common. Fatigue and rhinitis were rare, and recorded in only three cases.

	Tamsulosin group (N = 72)	Control group (N = 61)	p
Age (mean, SD)	33 + 5	36 + 6	> 0.05
Stone size, mm (mean, SD)	5.3 + 1.2	4.9 + 0.9	> 0.05
Stone clearance (in 4 weeks)	57 (79%)	20 (32%)	0.04 <sup>a</sup>
Stone clearance (in days)	12	18.5	0.02 <sup>a</sup>
Need for ESWL	15 (21%)	41 (68%)	0.4
Need for URS	1 (1.4%)	9 (15.6%)	0.4
Episodes of renal colic (4w)	2	6	0.003 <sup>a</sup>
Parenteral analgesia	0.5	4	0.004 <sup>a</sup>
Hospitalization	3 (4%)	11 (18%)	0.003 <sup>a</sup>

**Table 1:** Bivariate analysis for patients who received tamsulosin for stones 1-6 mm versus control group. <sup>a</sup>Statistically significant ( $p < 0.05$ ), SD: Standard Deviation, ESWL: Extracorporeal shock wave lithotripsy, URS: Ureteroscopy.

	Tamsulosin group (N = 91)	Control group (N = 86)	p <sup>a</sup>
Age (mean, SD)	33 + 5	36 + 6	> 0.05
Stone size, mm (mean, SD)	9.4 + 1.9	8.9 + 1.5	> 0.05
Stone clearance (in 4 weeks)	84 (92%)	56 (65%)	0.001 <sup>a</sup>
Stone clearance (in days)	27	51	0.03 <sup>a</sup>
Need for ESWL	45 (49%)	17 (20%)	0.003 <sup>a</sup>
Need for URS	6 (7%)	28 (33%)	0.001 <sup>a</sup>
Episodes of renal colic (4w)	4	11	0.003 <sup>a</sup>
Parenteral analgesia	1	9	0.005 <sup>a</sup>
Hospitalization	7 (8%)	34 (39%)	0.03 <sup>a</sup>

**Table 2a:** Bivariate analysis for patients who received tamsulosin as adjunctive therapy to ESWL for stone 6-12 mm versus control group.

	Exp (B)	95 % CI	Sig.
Stone clearance within 4weeks	3.6	1.2-5.8	0.00a
Need for ESWL	1.625	1.02-2.58	0.22a
Need for URS	5.14	1.7-6.2	0.00a

**Table 2b:** Binary logistic regression analysis for patients who received tamsulosin as adjunctive therapy to ESWL for stone 6-12 mm. aStatistically significant ( $p < 0.05$ ), SD: Standard Deviation, ESWL: Extracorporeal shock wave lithotripsy, URS: Ureteroscopy.

## Discussion

In our research, we studied the benefit of using tamsulosin on distal ureteric stones in two different settings to determine which patients may benefit from this medication. Tamsulosin achieved its maximum benefit when it was used as an adjunctive therapy to ESWL. It was pharmacologically identified that there is a heterogeneous distribution of  $\alpha_1$  adrenergic receptors (ARs) binding sites at the distal ureter.

With molecular characterization of alpha1 ARs subtypes were analyzed by semi-quantitative RT-PCR, Sigala et al found heterogeneous distribution of alpha1 AR binding sites, with the highest density of alpha1 ARs in the distal ureter and a lower density in the medial and proximal ureters [16]. This is the mechanism that was thought for tamsulosine [16,17]. Moreover, the ureter showed different patterns of alpha 1 receptor expression, (i.e. distal > medial = proximal), giving the molecular basis for the use of  $\alpha_1$  ARs antagonist in the expulsive therapy of distal ureter calculi [18]. Based on this data, different alpha blockers were studied in systematic reviews, silodosin was found to be superior to placebo as a medical expulsion therapy for distal ureteric stones [19]. In a similar study, alfuzosin was found to be safe and effective for stones smaller than 10-mm in size [7].

Besides alpha blockers, calcium channel blockers (CCBs) were tried to facilitate ureteric stones passage [20]. Experimental studies demonstrated that stones induce ureteral irritation with subsequent intra-cytoplasmic Ca influx, and ends with ureteral Clinical trials did not report the superiority of nifedipine over tamsulosin in the clearance of the distal ureteric stones [6].

Tamsulosin is a selective  $\alpha_1$  receptor antagonist that was thought to help patients who have distal ureter stones. In our study, and in the first group of patients who had distal ureteric stones, it helped in decreasing pain episodes of renal colic, analgesic use and hospitalization. In this group, tamsulosin did not show a greater benefit over the control group for stone clearance in multivariate analysis. This was reported by many series [6,14,15]. The minimal effect of tamsulosin on small stones could be explained by the possibility of spontaneous passage of those stones. Owing to the biological fact that there is a high likelihood of spontaneous passage of stones up to 5 mm, we would expect a minor effect of tamsulosin in the cases of lower ureteric stones.

For small distal ureteric stones, tamsulosin could help in

decreasing the need for analgesia. With the agreement of the finding from our study, Alizadeh M, et al. reported the same findings. In his study that comprised 96 patients with distal ureteral stones who were randomized into tamsulosin versus control; he found that the average amount of analgesic consumption in the control group was 2.3 +/- 4.31 and in the study group was 1.48 +/- 2.15 that showed significant differences ( $p < 0.05$ ) [23].

Pooled data in the literature are in favor of using tamsulosin post ESWL. The greatest benefit of using tamsulosin post ESWL, could be due to over-expression of alpha receptors, a matter that needs further experimental study. Additionally, similar results for steinstrasse were reported by Moursy et al and Bhagat SK, et al. [12,13]. Also, tamsulosin was effective in this group in our study.

Systematic review and clinical trials suggested that tamsulosin when used as an adjunctive therapy to ESWL, is safe and effective in enhancing stone expulsion. In a systematic review included twenty-one studies that investigated adjunctive tamsulosin therapy after ESWL, Chen et al. found that according to the stone locations (renal, upper and lower ureteral) and sizes (4-10 mm and 11-24 mm), tamsulosin is more useful for lower ureteral stone (RR: 1.28; 95% CI, 1.14-1.43) and larger sized stones (RR: 1.28 and 1.49 respectively) [9-11]. In accordance with these results, we found that the greatest benefit of using tamsulosin was noticed in this group. In this particular group, tamsulosin significantly reduced the time needed for stone clearance, the need for further ESWL sessions, and the need for URS. Tamsulosin reduced renal colic episodes, and the need for analgesic use.

Arrighi et al. studied alpha 1 adrenergic receptors and showed that there are evidences of both density and subtype gender-dependent expression. In our study, tamsulosin had the same effect on both sexes, as there was a statistically insignificant difference in all the groups between male and female patients.

As  $\alpha_1$  receptor antagonist, tamsulosin induces vasodilation, so headache and dizziness are expected side effects; moreover, it may induce retrograde ejaculation due to its effect on the  $\alpha_1$  receptor on the bladder neck. We reported 14/ 196 (6%) of tamsulosin adverse effects and in a meta-analysis conducted by Zhu y, et al. and among 484 patients, the adverse effects of tamsulosin were mainly dizziness that was reported in 3% of the patients [25].

Non-randomization and choosing a retrospective control groups and are the limitation of our study even if they were matched to the study groups. As matter of fact, our study was prospective, with a considerable number of patients who exhibited different stone settings in a single study.

## Conclusion

As a part of medical therapy for lower ureteric stones, tamsulosin showed the maximum benefit as an adjunctive therapy to ESWL for 6-12mm stones, and no benefit on stone passage for stones less than 6 mm in comparison to control groups.

## Compliance with Ethical Standards

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Ethical standards:** All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## References

- Romero V, Akpınar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol.* 2010;12(2-3):e86-96.
- Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, et al. 2007 Guideline for the management of ureteral calculi. *European urology.* 2007;52(6):1610-1631.
- Al-Naimi A, Alobaidy A, Majzoub A, Ibrahim TA. Evaluation of ureteroscopy outcome in a teaching hospital. *Turk J Urol.* 2016;42(3):155-161.
- Elbir F, Başbüyük İ, Topaktaş R, Kardaş S, Tosun M, Tepeler A, et al. Flexible ureterorenoscopy results: Analysis of 279 cases. *Turk J Urol.* 2015;41(3):113-118. doi: 10.5152/tud.2015.81488.
- Kirac M, Atkin MS, Biri H, Deniz N. Ureteroscopy: the first-line treatment for distally located ureteral stones smaller than 10 mm. *Urol J.* 2014;10(4):1028-1034.
- Pickard R, Starr K, MacLennan G, Lam T, Thomas R, Burr J, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet.* 2015;386(9991):341-349.
- Liu C, Zeng G, Kang R, Wu W, Li J, Chen K, et al. Efficacy and Safety of Alfuzosin as Medical Expulsive Therapy for Ureteral Stones: A Systematic Review and Meta-Analysis. *PLoS One.* 2015;10(8):e0134589. doi: 10.1371/journal.pone.0134589.
- Bhattar R, Jain V, Tomar V, Yadav SS. Safety and efficacy of silodosin and tadalafil in ease of negotiation of large ureteroscope in the management of ureteral stone: A prospective randomized trial. *Turk J Urol.* 2017;43(4):484-489. doi: 10.5152/tud.2017.83548.
- Chen K, Mi H, Xu G, Liu L, Sun X, Wang S, et al. The Efficacy and Safety of Tamsulosin Combined with Extracorporeal Shockwave Lithotripsy for Urolithiasis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of endourology.* 2015;29(10):1166-1176. doi: 10.1089/end.2015.0098.
- Wang H, Liu K, Ji Z, Li H. Effect of alpha1-adrenergic antagonists on lower ureteral stones with extracorporeal shock wave lithotripsy. *Asian J Surg.* 2010;33(1):37-41. doi: 10.1016/S1015-9584(10)60007-3.
- Zheng S, Liu LR, Yuan HC, Wei Q. Tamsulosin as adjunctive treatment after shockwave lithotripsy in patients with upper urinary tract stones: a systematic review and meta-analysis. *Scand J Urol Nephrol.* 2010;44(6):425-432. doi: 10.3109/00365599.2010.523014.
- Bhagat SK, Chacko NK, Kekre NS, Gopalakrishnan G, Antonisamy B, Devasia A. Is there a role for tamsulosin in shock wave lithotripsy for renal and ureteral calculi? *J Urol.* 2007;177(6):2185-2188.
- Moursy E, Gamal WM, Abuzeid A. Tamsulosin as an expulsive therapy for steinstrasse after extracorporeal shock wave lithotripsy: a randomized controlled study. *Scand J Urol Nephrol.* 2010;44(5):315-319. doi: 10.3109/00365599.2010.494616.
- Berger DA, Ross MA, Hollander JB, Ziadeh J, Chen C, Jackson RE, et al. Tamsulosin does not increase 1-week passage rate of ureteral stones in ED patients. *Am J Emerg Med.* 2015;33(12):1721-1724. doi: 10.1016/j.ajem.2015.08.006.
- Furyk JS, Chu K, Banks C, Greenslade J, Keijzers G, Thom O, et al. Distal Ureteric Stones and Tamsulosin: A Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial. *Ann Emerg Med.* 2016;67(1):86-95.e82. doi: 10.1016/j.annemergmed.2015.06.001.
- Sigala S, Dellabella M, Milanese G, Fornari S, Faccoli S, Palazzolo F, et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. *Neurourol Urodyn.* 2005;24(2):142-148.
- Itoh Y, Kojima Y, Yasui T, Tozawa K, Sasaki S, Kohri K. Examination of alpha 1 adrenoceptor subtypes in the human ureter. *Int J Urol.* 2007;14(8):749-753.
- Arrighi N, Bodei S, Zani D, Peroni A, Simeone C, Mirabella G, et al. [Alpha1 adrenoceptors in human urinary tract: expression, distribution and clinical implications]. *Urologia.* 2007;74(2):53-60.
- 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(1):13-22. doi: 10.1111/bcp.12737.
- Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of ureteral calculi. *Ann Emerg Med.* 2007;50(5):552-563.
- Borghi L, Meschi T, Amato F, Novarini A, Giannini A, Quarantelli C, et al. Nifedipine and methylprednisolone in facilitating ureteral stone passage: a randomized, double-blind, placebo-controlled

study. J Urol. 1994;152(4):1095-1098.

22.Sahin A, Erdemli I, Bakkaloglu M, Ergen A, Basar I, Remzi D. The effect of nifedipine and verapamil on rhythmic contractions of human isolated ureter. Arch Int Physiol Biochim Biophys. 1993;101(5):245-247.

23.Alizadeh M, Magsudi M. The effect of tamsulosin in the medical treatment of distal ureteral stones. Glob J Health Sci. 2014;6(7 Spec No):44-48. doi: 10.5539/gjhs.v6n7p44.

24.Picozzi SC, Marengi C, Casellato S, Ricci C, Gaeta M, Carmignani L. Management of ureteral calculi and medical expulsive therapy in emergency departments. J Emerg Trauma Shock. 2011;4(1):70-76. doi: 10.4103/0974-2700.76840.

25.Zhu Y, Duijvesz D, Rovers MM, Lock TM. alpha-Blockers to assist stone clearance after extracorporeal shock wave lithotripsy: a meta-analysis. BJU international. 2010;106(2):256-261. doi: 10.1111/j.1464-410X.2009.09014.x.

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