

Comparative efficacy of tamsulosin versus tadalafil as medical expulsive therapy for distal ureteric stones

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Abstract

Objective: The objective of this study was to compare the relative efficacy of tamsulosin and tadalafil as medical expulsive therapy for distal ureteric stones.

Patients and Methods: This was a prospective study performed between December 2014 and February 2016. A total of 123 adult patients (> 18 years of age) presenting with distal ureteric stones sized 6–10 mm were randomized to treatment with tamsulosin 0.4 mg once daily (Group A) or tadalafil 10 mg once daily (Group B). Therapy was given for a maximum of 4 weeks. The stone expulsion rate was the primary endpoint. Time to stone expulsion, number of colic episodes, analgesic use, number of hospital visits for pain, endoscopic treatment, and adverse effects of the drugs were noted. Statistical analyses were done using Fisher's exact test and Chi-square test.

Results: A total of 61 patients were included in tamsulosin group and 62 patients in tadalafil group. A statistically insignificant difference was found for stone clearance rate between both groups as a whole (Group A-73.77%, Group B-69.35%, $P = 0.690$) as well as when we considered both subgroups (A1-78.05%, B1-75.0%, $P = 0.802$; A2-65.0%, B2-55.6%, $P = 0.741$). All the primary and secondary outcome measures were more in favour of stones ≤ 8 mm size than stones > 8 mm size. No statistical difference was found for adverse drug effects except for retrograde ejaculation, which was significantly high in tamsulosin group ($P < 0.001$).

Conclusion: This study showed that although tamsulosin is more effective for stone clearance than tadalafil, but this difference was not significant ($P = 0.690$).

Keywords: Lower ureteric stones, medical expulsive therapy, tadalafil, tamsulosin

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INTRODUCTION


Medical expulsive therapy (MET) is an established noninvasive treatment modality for distal ureteric calculi. Varied combinations of medical treatments, including corticosteroid, nonsteroidal anti-inflammatory drug (NSAID), calcium-channel blocker, and α -adrenergic

blockers have been studied. Hollingsworth *et al.* found that there was a significant benefit for both calcium channel blockers and α -adrenergic blockers in improving stone passage rates.^[1] A subsequent meta-analysis performed by the American Urological Association (AUA)/European Association of Urology (EAU) ureteral stones guidelines

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panel found that α -adrenergic blockers were superior to nifedipine and may be the preferred agent for MET.^[2]

Drugs that expel stones might act by relaxing ureteral smooth muscle through inhibition of calcium channel pumps or α -1 receptor blockade.^[3,4] Tamsulosin is one of the most commonly used α -blockers.^[1,3,5-8] However, multiple studies have suggested that tamsulosin, terazosin, and doxazosin are equally effective, indicating a possible class effect.^[9-15]

Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms had already been demonstrated.^[16] With demonstration of *in vitro* effects of phosphodiesterase-5 inhibitor (PDE5i) sildenafil, vardenafil, and tadalafil on isolated human ureteral smooth muscle,^[17] interest in use of PDE5i as MET has increased.

Since alpha blockers, especially tamsulosin, are proven in multiple randomized controlled trials and in meta-analysis as well as recommended by EAU and AUA guidelines for use as MET for lower ureteric calculus of size up to 10 mm, role of PDE5i in this scenario is not so clear. Hence, we want to compare the efficacy of tadalafil, a PDE5i with the well-known drug tamsulosin.

PATIENTS AND METHODS

Between December 2014 and February 2016, 123 adult patients (>18 years of age) presenting with distal ureteric stones sized 6–10 mm were randomized using computer-based randomization charts equally into treatment with tamsulosin 0.4 mg once daily (Group A) or tadalafil 10 mg once daily (Group B). An informed and written consent was taken from each patient before enrolment into the study. Ethical clearance was taken from the institutional ethics committee. Stone size (largest transverse diameter) was measured on noncontrast computed tomography scan. Therapy was given for a maximum of 4 weeks. The stone expulsion rate, time to stone expulsion, analgesic use (NSAIDs), number of hospital visits for pain, follow-up and endoscopic treatment, and adverse effects of the drugs were noted. Both groups were further divided into two subgroups based on the stone size, one with stone size ≤ 8 mm and other with > 8 mm size. All outcome parameters were further compared among all subgroups to see any difference based on size if any.

Patients with solitary kidney, history of previous surgery on same ureter, UTI, deteriorating renal function, fever,

hydronephrosis, acute or chronic renal failure, multiple ureteral stones, a history of open surgery or endoscopic procedures in the urinary tract, allergy to tamsulosin or tadalafil, concomitant treatment with α -blockers, calcium antagonists, or nitrates, pregnant or lactating mothers, patients who demanded urgent stone removal were excluded from the study. Primary endpoint of this study was the stone expulsion rate. Statistical analysis was done using Fisher's exact test and Chi-square test.

RESULTS

A total of 124 patients were included in the study and randomized into two equal groups of 62 patients by the use of a computer-generated table. All patients completed the study except one in the tamsulosin group because of developing infected hydronephrosis during the study period. No statistically significant differences were observed regarding patients' age, sex, and stone size distribution between both groups [Table 1].

The stone expulsion rate was 73.77% in Group A and 69.35% in Group B. Although this was on the higher side in Group A, but the difference was not significant ($P = 0.69$). The mean expulsion time from the starting of MET was lower for tamsulosin group (9.38 ± 6.66 days) than for tadalafil group (9.61 ± 7.47 days), but this difference was also not significant ($P = 0.78$).

A number of colic episodes and analgesic use (NSAIDs) were significantly higher in tadalafil group than in tamsulosin group (0.96 ± 0.74 , 0.62 ± 0.83 , 0.010 ; 11.82 ± 3.34 , 9.15 ± 3.80 , 0.020), but the number of hospital visits was higher in tadalafil group ($P = 0.15$).

Table 1: Demographic information and results of the two groups

Parameter	Mean \pm SD		P
	Group A	Group B	
Age (years)	42.13 \pm 13.18	42.61 \pm 14.93	0.85
Gender			
Male	43	41	0.60
Female	18	21	
Stone size (mm)	7.54 \pm 1.11	7.60 \pm 0.91	0.74
Analgesic use*	9.15 \pm 3.80	11.82 \pm 3.34	0.02
Number of colic episodes [#]	0.62 \pm 0.83	0.96 \pm 0.74	0.01
Number of hospital visits [§]	0.51 \pm 0.22	0.39 \pm 0.26	0.15
Expulsion rate	73.77% (45/61)	69.35% (43/62)	0.69
Expulsion time (days) [§]	9.38 \pm 6.66	9.61 \pm 7.47	0.78

*Number of tablets of NSAIDs used during study period, [#]Number of colic episodes during the study period, [§]Number of hospital visits (OPD and IPD) during study period, [§]Days to stone expulsion from day of starting MET. SD: Standard deviation, NSAIDs: Nonsteroidal anti-inflammatory drugs, OPD: Outpatient department, IPD: Inpatient department, MET: Medical expulsive therapy

When we divided both groups into two subgroups based on the size of the stone, the only significant difference observed was for number of colic episodes and analgesic requirement in patients with stone size >8 mm. Patients in tadalafil group with stone size >8 mm had more colic episodes and they also required significantly more analgesics than patients in tamsulosin group ($P = 0.010$ and 0.032 , respectively). Patients with stone size ≤ 8 mm, more colic episodes, and analgesic requirements were in tadalafil group, but the difference was not significant. Rest of the primary and secondary outcome parameters compared among all subgroups were found to be in the favor of tamsulosin group, but these differences were statistically insignificant [Table 2].

Adverse effects such as headache and dizziness occurred more often in tadalafil group ($P > 0.05$), these were not significant enough to exclude the patients from the study. Incidence of orthostatic hypotension and backache was almost equal in both groups. Abnormal ejaculation was observed in 9.8% of patients in tamsulosin group and 1.6% of patients in tadalafil group with a highly significant difference ($P < 0.001$) [Table 3].

DISCUSSION

Of all urinary tract stones, 20% are ureteral stones, and 70% of these stones are located in the distal portion of the ureter.^[18,19] In last two to three decades, the introduction and improvement of new, minimally invasive procedures (extracorporeal shock wave lithotripsy and ureteroscopy) for ureteral stones has considerably changed the management of ureteral stones.^[20-22]

The majority of ureteral calculi can pass spontaneously and intervention is usually not required. It is estimated that 95% of stones up to 4 mm pass spontaneously within 40 days.^[2] A meta-analysis by the AUA guidelines panel determined that ureteral stones with a diameter of <5 mm will pass in up to 98% of cases. For stones with diameters >7 mm, the overall chance of spontaneous passage is low.^[23-25] A wide range of spontaneous passage rates have been reported, ranging from 71% to 98% for distal ureteral stones <5 mm

and 25%–53% for stones measuring 5–10 mm with a mean expulsion time of >10 days.^[2,3]

Most authors recommend that stone passage should not exceed 4–6 weeks due to the risk of renal damage.^[25] Conservative management is less appropriate in patients with prolonged partial ureteral obstruction (>4–6 weeks), persisting pain or urinary tract infection. Hence, observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function). Both the European (EAU) and AUA guidelines also recommend alpha blockers as a viable option in these cases.^[2,3,26]

Many medical therapies have been investigated as METs including alpha blockers, calcium channel blockers, corticosteroids, and most recently PDE5i. Alpha blockers are currently the only recommended monotherapy for use as MET. Due to the high likelihood of spontaneous passage of stones up to ~5 mm, MET is less likely to increase the stone-free rate in these cases.^[3] However, MET reduces the need for analgesics in small stones.^[1,3,4]

In a randomized trial of combination therapy including a corticosteroid with tamsulosin compared with corticosteroid with an antispasmodic fluoroglucine trimetossibenzene, Dellabella *et al.* found an increased expulsion rate (70% vs. 100%), more rapid stone expulsion time (111.1 compared with 65.7 h) and less requirement for analgesia in the group treated with tamsulosin for juxtavesical ureteral stones (around 4–13 mm).^[20] In the present study, stone expulsion rate in patients treated with tamsulosin was 73.77% and expulsion time was 9.38 ± 6.66 days which is comparable with the earlier studies.^[1,27]

PDEi are a class of drugs that inhibit the breakdown of cAMP and cGMP, enhancing smooth muscle relaxation. Therefore, PDEi may be able to decrease ureteral spasm and facilitate stone passage. Tadalafil is a selective PDE5i and because of its smooth muscle relaxation property, tadalafil received the US Food and Drug Administration approval for lower urinary tract symptoms with benign prostatic hyperplasia and erectile dysfunction.^[28,29]

Table 2: Comparison of primary and secondary outcome parameters among subgroups

Parameter	Group A1 (tamsulosin ≤ 8 mm)	Group B1 (tadalafil ≤ 8 μ m)	P	Group A2 (tamsulosin >8 μ m)	Group B2 (tadalafil >8 μ m)	P
Analgesic use*	8.90 \pm 3.12	9.65 \pm 3.17	0.542	9.7 \pm 3.8	14.17 \pm 2.50	0.032
Number of colic episodes#	0.53 \pm 0.63	0.66 \pm 0.57	0.111	1.05 \pm 0.81	1.76 \pm 0.81	0.010
Number of hospital visits [§]	0.15 \pm 0.42	0.11 \pm 0.32	0.690	0.50 \pm 0.61	0.67 \pm 0.48	0.205
Expulsion rate	78.05% (32/41)	75.0% (33/44)	0.802	65.0% (13/20)	55.6% (10/18)	0.741
Expulsion time (days) [§]	11.47 \pm 3.60	12.36 \pm 3.53	0.735	15.77 \pm 3.90	18.80 \pm 4.19	0.233

*Number of tablets of NSAIDs used during study period, #Number of colic episodes during the study period, §Number of hospital visits (OPD and IPD) during study period, §Days to stone expulsion from day of starting MET. NSAIDs: Nonsteroidal anti-inflammatory drugs, OPD: Outpatient department, IPD: Inpatient department, MET: Medical expulsive therapy

Table 3: Side effects

Parameter	Group A (%)	Group B (%)	P
Headache	6 (9.8)	7 (11.3)	0.83
Dizziness	4 (6.6)	6 (9.7)	
Backache	3 (4.92)	3 (4.8)	
Orthostatic hypotension	2 (3.28)	2 (3.2)	
Abnormal ejaculation	6 (9.8)	1 (1.6)	<0.001

In this study, it was found that the stone expulsion rate and time required with tadalafil were better than historical controls (25%–54% and >10 days) but inferior to tamsulosin (73.77% and 9.38 ± 6.66 days for tamsulosin vs. 69.35% and 9.61 ± 7.47 days for tadalafil: $P = 0.775$).^[16,27] The reason behind this lower efficacy of tadalafil may be due to the predominance of alpha receptors than PDE5 in lower ureter.

A ureteral stone usually causes severe colicky pain as a result of an increase in intraureteral pressure above the site of ureteral obstruction. At present, NSAIDs and anti-spasmodic drugs are generally used for relieving the pain caused by acute ureteral obstruction. Tamsulosin and tadalafil might reduce the colicky episodes, hence analgesics requirement and hospital visits by relaxing the ureteral smooth muscles and early stone expulsion.^[29,30] In our study, number of colic episodes, analgesics requirement, and number of hospital visits were lower in tamsulosin group than in tadalafil group (0.62 ± 0.83 ; 9.15 ± 3.80 ; 0.22 ± 0.51 , respectively, for tamsulosin group vs. 0.96 ± 0.74 ; 11.82 ± 3.34 ; 0.26 ± 0.39 for tadalafil).

In our best knowledge, no study till date had compared tamsulosin and tadalafil after dividing them into subgroups based on the stone size. In the present study, it was found that tamsulosin was better than tadalafil for all primary and secondary outcome variables and this difference was more for stones >8 mm sizes.

No serious side effect occurred in any patient. Headache and dizziness were more common in tamsulosin group while the incidence of backache and orthostatic hypotension was almost similar in both groups. Abnormal ejaculation was significantly higher in tamsulosin group (9.8% vs. 1.6%; $P < 0.001$). Limitations of this study were small sample size and single-center-based study.

CONCLUSION

Medical expulsion therapy using tamsulosin and tadalafil is efficacious and safe for lower ureteric calculus up to 10 mm size. This study showed that although tamsulosin is more effective for stone clearance than tadalafil, but this difference was not significant ($P = 0.690$). Furthermore,

the side effects with tamsulosin were found to be less than that with tadalafil. Further large multicenter randomized controlled trials are needed for validation of these results.

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Conflicts of interest

There are no conflicts of interest.

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