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

Suresh Kumar Goyal, Vikash Singh, Himanshu Pandey¹, Mahaveer Kumar Chhabra, Satinder Pal Aggarwal², Amilal Bhat

Department of Urology, Dr. S. N. Medical College, ¹Department of Urology, All India Institute of Medical Sciences, Jodhpur, ²Department of Urology, S.M.S. Medical College, Jaipur, Rajasthan, India

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

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 \( \alpha \)-adrenergic blockers have been studied. Hollingsworth et al. found that there was a significant benefit for both calcium channel blockers and \( \alpha \)-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

How to cite this article: Goyal SK, Singh V, Pandey H, Chhabra MK, Aggarwal SP, Bhat A. Comparative efficacy of tamsulosin versus tadalafil as medical expulsive therapy for distal ureteric stones. Urol Ann 2018;10:82-6.
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.\[1,3,5,6\] However, multiple studies have suggested that tamsulosin, terazosin, and doxazosin are equally effective, indicating a possible class effect.\[9,10\]

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

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. 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. 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.

Most authors recommend that stone passage should not exceed 4–6 weeks due to the risk of renal damage. 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.

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. However, MET reduces the need for analgesics in small stones.

In a randomized trial of combination therapy including a corticosteroid with tamsulosin compared with corticosteroid with an antispasmodic fluoroglucline trimetossibenzenze, 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). 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.

PDE5i are a class of drugs that inhibit the breakdown of cAMP and cGMP, enhancing smooth muscle relaxation. Therefore, PDE5i 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.
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 intratueral 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.[29,38] 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.

Acknowledgment

We acknowledge the support of Er. Rajesh Goyal, Dr. Chandan Jha, and Dr. Vikram Aggarwal.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Hollingsworth JM, Rogers MA, Kaufman SR, Bradford TJ, Saint S, Wei JT, et al. Medical therapy to facilitate urinary stone passage: A meta-analysis. Lancet 2006;368:1171-9.
2. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, et al. 2007 Guideline for the management of ureteral calculi. Eur Urol 2007;52:1610-31.
3. Seitz C, Liatsikos E, Porgiglia F, Tiselius HG, Zwergel U. Medical therapy to facilitate the passage of stones: What is the evidence? Eur Urol 2009;56:455-71.
4. Liatsikos EN, Katsakiori PF, Assimakopoulos K, Voudoukis T, Kallidonis P, Constantinides C, et al. Doxazosin for the management of distal-ureteral stones. J Endourol 2007;21:538-41.
5. Lojanapiwat B, Kochakarn W, Suparatchapun N, Lertwuttichakul K. Effectiveness of low-dose and standard-dose tamsulosin in the treatment of distal ureteric stones: A randomized controlled study. J Int Med Res 2008;36:529-36.
6. Wang CJ, Huang SW, Chang CH. Efficacy of an alpha1 blocker in expulsive therapy of lower ureteral stones. J Endourol 2008;22:41-6.
7. Kaneko T, Matsushima H, Morimoto H, Tsuzaka Y, Homma Y. Efficacy of low-dose tamsulosin in medical expulsive therapy for ureteral stones in Japanese male patients: A randomized controlled study. Int J Urol 2010;17:462-5.
8. Al-Ansari A, Al-Naimi A, Alohabdy A, Assadiq K, Azmi MD, Shokeir AA. Efficacy of tamsulosin in the management of lower ureteric stones: A randomized double-blind placebo-controlled study of 100 patients. Urology 2010;75:6-7.
9. Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of 3 different alpha1- adrenergic blockers for distal ureteric stones. J Urol 2005;173:2010-2.
10. Zehni AA, Ather MH, Abbas F, Bijabani SR. Preliminary study of efficacy of doxazosin as a medical expulsive therapy of distal ureteric stones in a randomized clinical trial. Urology 2010;75:1285-8.
11. Agrawal M, Gupta M, Gupta A, Agrawal A, Sarkari A, Lavania P, et al. Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral stones. Urology 2009;73:706-9.
12. Pedro RN, Hinck B, Hendlin K, Feik K, Canales BK, Monga M, et al. Alfuzosin stone expulsion therapy for distal ureteral calculi: A double-blind, placebo controlled study. J Urol 2008;179:2244-7.
13. Chau LH, Tai DC, Fung BT, Li JC, Fan CW, Li MK. Medical expulsive therapy using alfuzosin for patient presenting with ureteral stone less than 10 mm: A prospective randomized controlled trial. Int J Urol 2011;18:510-4.
14. Zhou SG, Lu JL, Hui JH. Comparing efficacy of a1D-receptor antagonist naftopidil and a1A/D-receptor antagonist tamsulosin in management of distal ureteral stones. World J Urol 2011;29:767-71.
15. Tsuzaka Y, Matsushima H, Kaneko T, Yamaguchi T, Homma Y.
Goyal, et al.: Tamsulosin versus tadalafil as medical expulsive therapy

Naftopidil vs. silodosin in medical expulsive therapy for ureteral stones: A randomized controlled study in Japanese male patients. Int J Urol 2011;18:792-5.

16. Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L, et al. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. Eur Urol 2012;61:917-25.

17. Gratze C, Uckert S, Kedia G, Reich O, Schlenker B, Seitz M, et al. In vitro effects of PDE5 inhibitors sildenafil, vardenafil and tadalafil on isolated human ureteral smooth muscle: A basic research approach. Urol Res 2007;35:49-54.

18. Küpeli B, Irkilata I, Gürocak S, Tunç I, Kiracı M, Karaoglan U, et al. Does tamsulosin enhance lower ureteral stone clearance with or without shock wave lithotripsy? Urology 2004;64:1111-5.

19. Carstensen HE, Hansen TS. Stones in the ureter. Acta Chir Scand Suppl 1973;433:66-71.

20. Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. J Urol 2003;170 (6 Pt 1):2202-5.

21. Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. J Urol 1997;158:1915-21.

22. Menon M, Resnick MI. Urinary lithiasis: Etiology, diagnosis, and medical management. In: Walsh PC, Retik AB, Vaughan ED, editors. Campbell’s Urology. Philadelphia: Saunders; 2002. p. 3227-92.

23. Stoller ML, Bolton DM. Urinary stone disease. In: Tanagno EA, McAninch JW, editors. Smith’s Urology. San Francisco: Lange Medical Book/McGraw-Hill; 2000. p. 291-320.

24. Ibrahim AI, Shetty SD, Awad RM, Patel KP. Prognostic factors in the conservative treatment of ureteric stones. Br J Urol 1991;67:358-61.

25. Tiselius HG, Ackermann D, Alken P, Buck C, Conort P, Gallucci M, et al. Guidelines on urolithiasis. Eur Urol 2001;40:362-71.

26. Turk C, Knoll T, Petrik A. Guidelines on Urolithiasis. European Association of Urology; 2014. Available from: http://www.uroweb.org/gls/pdf/%Urolithisis_LR.pdf. [Last accessed on 2014 Dec 01].

27. Kumar S, Jayant K, Agrawal S, Singh SK. Comparative efficacy of tamsulosin versus tamsulosin with tadalafil in combination with prednisolone for the medical expulsive therapy of lower ureteric stones: A randomized trial. Korean J Urol 2014;55:196-200.

28. Shabsigh R, Sefel AD, Rosen RC, Porst H, Abuja S, Deeley MC, et al. Review of time of onset and duration of clinical efficacy of phosphodiesterase type 5 inhibitors in treatment of erectile dysfunction. Urology 2006;68:689-96.

29. Setter SM, Ittz JL, Fincham JE, Campbell RK, Baker DE. Phosphodiesterase 5 inhibitors for erectile dysfunction. Ann Pharmacother 2005;39:1286-95.

30. Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. AJR Am J Roentgenol 2002;178:101-3.