



Comparative Efficacy of Tamsulosin Versus Tamsulosin With Tadalafil in Combination With Prednisolone for the Medical Expulsive Therapy of Lower Ureteric Stones: A Randomized Trial

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Purpose: To compare the safety and efficacy of tamsulosin and tamsulosin with the phosphodiesterase-5 inhibitor tadalafil in combination with prednisolone as medical expulsive therapies for lower ureteric stones.

Materials and Methods: Between July 2011 and December 2012, 62 adult patients presenting with distal ureteric stones sized 5 to 10 mm were randomized equally to treatment with tamsulosin (group A) or tamsulosin with tadalafil (group B). Therapy was given for a maximum of 6 weeks. In addition, patients in groups A and B were given 5-mg prednisolone once daily (maximum 1 week). The stone expulsion rate, time to stone expulsion, analgesic use, number of hospital visits for pain, follow-up and endoscopic treatment, and adverse effects of the drugs were noted. Statistical analyses were done by using Student t-test and chi-square test.

Results: There was a higher expulsion rate (83.9% in group B and 74.2% in group A) and a lower time to expulsion in both treatment groups than in historical controls used in earlier studies. However, these results were not statistically significant ($p=0.349$, $p=0.074$, respectively). Statistically significant differences were noted in hospitalization for colic and analgesic requirement, which were less in group B than in group A. There were no serious adverse events. Another important finding was improvement in erectile function in group B.

Conclusions: Medical expulsive therapy for distal ureteric stones using tamsulosin and tadalafil with prednisolone is safe and efficacious. Also, the prescription of tadalafil in cases of erectile dysfunction with the development of lower ureteric stones may provide additional advantages.

Keywords: *Prednisolone; Tadalafil; Tamsulosin; Urinary calculi*

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INTRODUCTION

The incidence of urinary stones has been increasing day by day. This may partially be attributed to better quality of life. Stone incidence also varies with race, ethnicity, and geographic region. Men are affected twice as commonly as women, with peak incidence being at 30 years of age. Ureteral stones contribute to 20% of all urinary tract stones, 70% of which are located in the distal ureter. Fifty

percent of patients have a recurrence of renal colic within 5 years of the first episode. Urolithiasis is a chronic disease with substantial economic consequences and great public health importance [1].

Medical expulsive therapy developed after an understanding of the various physiologic and pathophysiologic bases for urinary stones. The ureter is lined by smooth muscle cells with alpha-1 adrenergic receptors, especially in the distal third. Receptor blockade inhibits both basal smooth

muscle tone and hyperperistaltic uncoordinated frequency in order to maintain tonic propulsive contractions. Ureteric calculi can induce ureteric spasms that interfere with expulsion; thus, muscle relaxation while maintaining normal peristaltic activity may facilitate passage [2,3]. Therefore, alpha-1 adrenergic receptor antagonists work by creating an increased pressure gradient around the stone, which propels distal ureteral stones out of the ureter. Tamsulosin has a proven role in increasing the stone expulsion rate and in decreasing expulsion time [4,5]. Finally, it has been shown that ureteral calculi induce intense inflammatory changes and submucosal edema in proximity to a stone that may worsen ureteric obstruction, thus increasing the risk of impaction and retention. Thus, steroids can facilitate stone expulsion by reducing the submucosal edema.

Recently, tadalafil, which is a phosphodiesterase-5 (PDE5) inhibitor, was shown to act by a nitric oxide/cyclic guanosine monophosphate (cGMP)-signaling pathway, resulting in increased levels of cGMP, leading to smooth muscle relaxation in the ureter [6]. Owing to its smooth muscle relaxation property, tadalafil received approval from the Food and Drug Administration for lower urinary tract symptoms associated with benign prostatic hyperplasia and erectile dysfunction. Daily dosing with 10 mg has shown better results and tolerance than 20 mg per day [7].

By combining drugs acting through different mechanisms, we can achieve better ureteric relaxation and reduction in intramural pressure, which will facilitate stone passage. This was our main aim in studying the use of tadalafil along with tamsulosin.

MATERIALS AND METHODS

The study was performed in a tertiary care institute in Chandigarh, India, after the study investigators received clearance from the institutional ethics committee. Between July 2011 and December 2012, all patients older than 18 years of age with a ureteral stone 5 mm to 10 mm in size situated below the common iliac vessels as diagnosed by noncontrast computed tomography were included in the study if their pain was relieved with diclofenac injection within 1 day. Patients with fever, hydronephrosis, acute or chronic renal failure, multiple ureteral stones, a history of open surgery or endoscopic procedures in the urinary tract, diabetes, peptic ulcer, or concomitant treatment with β -blockers, calcium antagonists, or nitrates; pregnant or lactating mothers; and patients who demanded urgent stone removal were excluded. Sample size was calculated a priori with the alpha level set at 0.05, an anticipated effect size (Cohen's *d*) of 0.65, and a desired statistical power level of 0.8. The required sample size per group was 30. Unpaired t-test tests and chi-square tests were used for the analysis of the variables and categorical data. Differences were considered significant at a p-value of less than 0.05.

Seventy patients were enrolled in the study, of whom 64

were studied, as the rest did not satisfy the inclusion criteria. Written informed consent was obtained and the patients were simply randomized into two equal groups of 32 patients by use of a computer-generated table. The randomization table was stored centrally and the group assigned to each patient was conveyed to the author. Patients in group A were given tamsulosin 0.4 mg once daily, and those in group B were given tamsulosin 0.4 mg and tadalafil 10 mg once daily. In addition, patients in groups A and B received prednisolone 5 mg once daily for 1 week. In both groups, drugs were continued until stone expulsion or for a maximum of 6 weeks. During the study, one patient in each group dropped out. All patients were evaluated by physical examination; serum creatinine; urine culture; plain x-ray of the kidneys, ureters, and bladder (KUB); ultrasonography; and noncontrast computed tomography of the KUB region. All patients presenting with ureteral colic were given pain relief with intramuscular diclofenac. Patients were instructed to filter their urine by using a standard mesh net to detect stone expulsion. The expulsion time; analgesic use; number of hospital visits for pain, follow-up, and endoscopic treatment; and adverse effects of drugs were noted. The maximum duration of follow-up was 6 weeks, after which patients underwent semirigid ureterorenoscopy for removal of stones that were not expelled. The primary outcome studied was the stone expulsion rate. Secondary endpoints were stone expulsion time, number of pain episodes, analgesic use, and self-reported side effects related to medical therapy. Expulsion of the stone was confirmed with plain x-ray, ultrasonography, or noncontrast computed tomography.

Discrete variables were taken as counts (or frequencies) and were evaluated by chi-square test. Continuous variables with normal distributions were presented as mean \pm standard deviations and were compared by unpaired Student t-tests. Data were entered into a Microsoft Excel worksheet (Microsoft Co., Redmond, WA, USA) and were analyzed by using SPSS ver. 17 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

All patients completed the study. No statistically significant differences were observed between the groups regarding age, gender, or stone size distribution (Table 1).

The stone expulsion rate was 74.2% in group A and 83.9% in group B. Although the stone expulsion rate was on the higher side in group B, the difference was not statistically significant (p=0.349). The mean expulsion time trended toward a lower value in group B (15.15 \pm 5.5 days) than in group A (18.9 \pm 8.7 days), but this difference was also not significant (p=0.074).

The average number of hospital visits for colicky pain were comparatively fewer in group B (0.45 \pm 0.67) than in group A (2.90 \pm 0.90), and this difference was highly significant (p=0.000). Also, the mean analgesic requirement

TABLE 1. Demographic information and results of the two groups

Parameter	Group A	Group B	p-value
Age (y)	32.45±9.36	35.23±13.54	0.352 ^a
Gender			0.093 ^b
Male/female	19/12	25/6	
Stone size (mm)	7.05±1.62	6.67±1.44	0.337 ^a
Expulsion rate (%)	74.2 (23/31)	83.9 (26/31)	0.349 ^b
Expulsion time (d)	18.90±8.71	15.15±5.40	0.074 ^a
Analgesic uses	2.90±0.90	1.87±1.38	0.000 ^a
No. of colic	1.60±1.00	0.45±0.68	0.001 ^a
Duration of follow-up (wk)	3.94±1.52	3.06±1.39	0.043 ^a
No. of hospital visits	3.85±0.99	2.90±0.90	0.010 ^a

Values are presented as mean±standard deviation unless otherwise indicated.

Group A, tamsulosin and prednisolone; Group B, tamsulosin, tadalafil, and prednisolone.

^a:Statistical significance was analyzed by Student t-test. ^b:Statistical significance was analyzed by chi-square test.

TABLE 2. Adverse effects in each group

Parameter	Group A	Group B	p-value
Headache	12.9%	16.1%	0.718
Dizziness	12.9%	16.1%	0.718
Backache	9.6%	16.1%	0.420
Orthostatic hypotension	3.0%	6.4%	0.627
Rate of abnormal ejaculation	19.4%	12.9%	0.490
Improvement in erectile dysfunction	0%	12.9%	-

Group A, tamsulosin and prednisolone; Group B, tamsulosin, tadalafil, and prednisolone.

was significantly less in group B (1.87±1.38 times) than in group A (2.90±0.90 times) ($p < 0.0001$).

Although side effects such as headache, dizziness, orthostatic hypotension, and backache occurred more often in group B patients ($p > 0.05$), these were not significant enough to exclude the patients from the study. Abnormal ejaculation was observed in 19.4% of patients in group A and 12.9% of patients in group B, which was not a significant difference ($p = 0.489$). Another important finding to note was that none of the patients in group A experienced any changes in erectile function, whereas 12.9% of the patients in group B experienced improvement (Table 2).

DISCUSSION

Urolithiasis is one of the most common urologic diseases. Among all urinary tract stones, 20% are ureteral stones, of which 70% are found in the lower third of the ureter [8].

The factors influencing spontaneous expulsion are stone location, size, number, and structure; ureteral spasm; mucosal edema or inflammation; and ureteral anatomy. Therefore, the use of medical therapy is justifiable to reduce edema, reduce spasm, and relax the smooth muscles for stone expulsion [9,10].

Current therapeutic options for distal ureteral stones include active intervention as well as conservative wait and watch approaches. The efficacy of mini-invasive therapies,

such as extracorporeal shock wave lithotripsy and ureterorenoscopy, has been proven by several studies [11,12]. Although such procedures are effective, they are not free from risk or inconvenience and have consequent implications such as lowering the quality of life, high cost, and suspension of regular activities [13].

According to data in the literature, the distal ureteric stone expulsion rate with the watchful waiting approach is 25% to 54% with a mean expulsion time of greater than 10 days and considerable analgesic requirement, even for stones < 4 mm.

To increase the expulsion rate and reduce the analgesic requirement, there is a great deal of enthusiasm for adjuvant pharmacological interventions [14]. Conservative therapy is considered, especially in cases of distal ureteral stones. In 2005, Sigala et al. [15] found that α -1D and α -1A adrenoceptors are present in significantly larger amounts than α -1B adrenoceptors in the human ureter. Therefore, clinical studies have been conducted to investigate the effect of the combined α -1A- and α -1D-selective antagonist tamsulosin on distal ureteral stone expulsion. Most of these studies showed that tamsulosin treatment improves the expulsion rate of medium-sized (3–10 mm) stones. We also observed an expulsion rate of 74.2% with tamsulosin, which was better than the expulsion rates in historical controls used in earlier studies of 43% and 30.2% [16-19]. Thus, tamsulosin represents a noninvasive and cost-effective al-

ternative to interventional approaches. Although medical expulsive therapy has become a standard treatment option, it is still underused by physicians in emergency departments [20].

We decided to use tadalafil on the basis of reports by Gratzke et al. [21] who demonstrated the role of phosphodiesterase inhibitors in relaxation of ureteric muscles in the rank order of vardenafil > sildenafil > tadalafil [22,23]. Because tadalafil is more selective than sildenafil for PDE5 than PDE6 receptors, which are present in the retina, visual problems are less likely. Tadalafil has the longest duration of action (~36 hours with a half-life of 17.5 hours) among the current PDE5 inhibitors, and its activity is unaffected by meals. Vardenafil has a structure similar to that of sildenafil, but the structure of tadalafil is quite different [24,25]. To keep adverse effects to a minimum, we used tadalafil in smaller doses (10 mg). Another reason to choose tadalafil with tamsulosin was because Klöner et al. [26,27] demonstrated that the combination of tamsulosin+tadalafil did not show significant hemodynamic changes. This combination had also been used for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia by Bechara et al. [28] and has shown significant improvements in pain by the relaxation of the bladder, urethra, and prostate and was the basis of this pilot study. We also combined prednisolone (5 mg) in both groups because of its antiedemic property.

With regard to the primary end point of our trial, both groups compared in our study proved superior to the historical controls who were treated by the watchful waiting approach. We did not use a placebo or control group in the present study, because our objective was to prospectively compare the efficacy of these two groups, which included drugs that may modulate the motility of the obstructed ureter. We observed an apparently higher expulsion rate and lower expulsion time in group B than in group A; however, these results were not statistically significant [83.9%, 15.15±5.4 days (range, 7–27 days) compared with 74.2%, 18.9±8.7 days (range, 15–35 days); $p=0.349$ and $p=0.074$]. The possible explanation for these better results may be the combined spasmolytic effect of these medications on the ureter, whereas prednisolone reduces edema and decreases inflammation.

Our results did not reach statistical significance, probably because of the small sample size. This study was undertaken as a pilot project. Thus, because such studies have not been conducted earlier, we could not perform a formal sample size calculation.

Colicky pain in ureteral stones occurs owing to an increase in intraureteral pressure above the site of ureteral obstruction. Kinnman et al. [29] found that α -blockade may relieve ureteric colic by blocking the C-fibers responsible for mediating pain. Use of α -blockers for expulsion of ureteric stones probably decreases the analgesic requirement in two ways: expulsion of stones and blockade of C-fibers. Thus, it is difficult to assess which of these may be primarily responsible for decreasing the analgesic requirement.

In our study, the analgesic requirement in group B was significantly less than that in group A ($p=0.001$). This excellent pain control observed in group B patients was also demonstrated by the lesser need for hospitalization for colic during the study. These effects of the combined use of tamsulosin and tadalafil on the ureter were probably due to a decrease in the frequency and amplitude of the phasic peristaltic contractions that accompany ureteric obstruction, i.e., an improved antispasmodic effect.

The reported side effects were minimal in our study, probably because of the younger study population and the lack of any associated comorbidity. The use of a near physiological dose of prednisolone and the careful exclusion of patients with contraindications to steroids may explain the lack of significant side effects related to steroid use [30]. The 5-mg dose of prednisolone is nearly five times lower than the 30-mg deflazacort dose used in previous studies. Although abnormal ejaculation was observed in 19.4% of patients in the tamsulosin and prednisolone group A and 12.9% of patients in the tadalafil group B, this difference was not significant ($p=0.489$).

Even though this study was not designed to demonstrate the association of drugs for the treatment of erectile dysfunction, we found improvement in erectile function in 12.9% of patients (i.e., 4 patients) in group B, whereas none of the patients in group A experienced any change. In the data analysis, we found that these patients were in the age group of between 46 and 48 years. The limitation of our study was the small sample size, but the study is still valuable as a pilot study. Furthermore, to our knowledge, this is the comparison study of tamsulosin with tamsulosin and tadalafil and produced some insightful results that should be tested in future studies.

CONCLUSIONS

The results of this study indicate that the addition of tadalafil with tamsulosin and prednisolone increases the ureteric stone expulsion rate, although not significantly so, and provides significant control of pain, a significantly lesser analgesic requirement, and fewer hospital visits. Also, the prescription of tadalafil in cases of erectile dysfunction with the development of lower ureteric stones may provide an additional advantage in the expulsion of stones.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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