

Comparative efficacy of tadalafil *versus* tamsulosin as the medical expulsive therapy in lower ureteric stone: a prospective randomized trial

Sandeep Puvvada, Prasad Mylarappa, Kuldeep Aggarwal, Avinash Patil, Prarthan Joshi, Ramesh Desigowda

MS Ramaiah Medical College, Bangalore, Karnataka, India

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Corresponding author

Sandeep Puvvada

Department of Urology

MS Ramaiah Medical College

Bangalore, Karnataka

India

dr.sandeep001@gmail.com

Introduction In recent years, medical expulsive therapy has been used in the management of distal ureteric stones as a supplement to conservative treatment. Therefore, we conducted a prospective randomized study to evaluate the possible role of tadalafil individually in comparison with proven tamsulosin therapy in ureteric stone expulsion.

The aim of this study is to compare the safety and efficacy of a phosphodiesterase-5 inhibitor (tadalafil) and an α -1 blocker (tamsulosin) as medical expulsive therapy for distal ureteric calculi.

Material and methods Between August 2014 and October 2015, 207 patients who presented with distal ureteric stones of size 5–10 mm were randomly divided into two groups: tadalafil (Group A) and tamsulosin (Group B). Therapy was given for a maximum of 4 weeks. Stone expulsion rate, time to stone expulsion, analgesic use, number of hospital visits for pain, follow-up, endoscopic treatment and adverse effects of drugs were noted. Both groups were compared for normally distributed data by percentage, analysis of variance, and T-test. All the classified and categorical data were analyzed for both groups using the chi-square test.

Results A statistically significant expulsion rate of 84.0% in Group A compared with 68.0% in Group B (P value = 0.0130), and shorter stone expulsion time in Group A (14.7 ± 3.8) in comparison to Group B (16.8 ± 4.5) was observed. Statistically significant differences were noted in renal colic episodes and analgesic requirement in Group A than Group B. No serious adverse effects were noted.

Conclusions Tadalafil is safe, efficacious, and well tolerated as medical expulsive therapy for distal ureteric stones. This study showed that tadalafil increases ureteric stone expulsion quite significantly along with better control of pain and significantly lower analgesic requirement.

Key Words: tadalafil *versus* tamsulosin \leftrightarrow medical expulsive therapy \leftrightarrow lower ureteric stone

INTRODUCTION

Urolithiasis is one of the most common disorders of the urinary tract and the prevalence of stone disease has been estimated at 10% to 15% in the United States [1]. This may partially be attributed to better quality of life. The probability of having a stone also varies according to age, gender, race, and geographic location. Renal stones are most prevalent between the ages of 20 and 40 years and are

3 times more common in men than women [2]. Women excrete more citrate and less calcium than men, which partially explains the higher incidence of stone disease in men. Twenty-two percent of all urinary tract stones are found in the ureter, of which 68% are seen in the distal ureter [3].

The best treatment modality depends upon various factors such as size, localization and composition of the stone, severity of obstruction, symptoms, and anatomy of the urinary system. The watchful

waiting approach can result in complications, such as infection of the urinary tract, hydronephrosis, and deranged renal function. Ureteric stones have been treated traditionally with interventional techniques like ureteroscopy or open surgery. In recent years, medical expulsive therapy (MET) has been used in the management of distal ureteric stones as a supplement to conservative treatment.

The ureter is lined by α -1 adrenergic receptors, particularly the subtype α -1D, which are more concentrated in its distal third section, and they play an important role in the lower ureteric physiology through an effect on detrusor and ureteric smooth muscle contraction. Blocking these receptors subsequently induces selective relaxation of the ureteric smooth muscle, which will result in ureteric lumen dilatation facilitating antegrade stone propagation [4, 5]. Tamsulosin, a selective alpha-blocker with equal affinity for both α -1A and α -1D receptors, has a proven role in MET in increasing the stone expulsion rate and decreasing expulsion time [6, 7].

A newly launched phosphodiesterase-5 (PDE-5) inhibitor, tadalafil, has emerged which acts on the NO/cGMP-signaling pathway of smooth muscles, resulting in increased levels of cyclic guanosine monophosphate, causing ureteric relaxation. Due to its smooth muscle relaxation property, tadalafil was approved by the FDA for use in lower urinary tract symptoms in patients with benign prostatic hyperplasia and erectile dysfunction. It also received FDA approval for use in pulmonary arterial hypertension for both men and women [8, 23].

Therefore, we conducted a prospective randomized study to evaluate the efficacy and safety of tadalafil individually and also in comparison with tamsulosin for ureteric stone expulsion.

MATERIAL AND METHODS

This study was conducted in our hospital after receiving clearance from the institutional ethics committee. It was conducted over a period of 15 months from August 2014 to October 2015. After obtaining written informed consent, patients aged ≥ 18 years with a ureteral stone size of 5-10 mm in its greatest dimension and situated below the common iliac vessels, as diagnosed by non-contrast computed tomography of the kidney, ureter, and bladder (KUB) were included in this study. Patients were only included if their pain was relieved with diclofenac injection within 1 day. Patients with fever, hydronephrosis, acute or chronic renal insufficiency, multiple ureteral stones, open surgery or endoscopic interventions, diabetes, peptic ulcer or on concomitant treatment with β -blockers, calcium antagonists, or nitrates;

pregnant or lactating mothers; or patients who demanded immediate intervention were excluded.

Sample size was calculated a priori with the alpha level set at 0.05, an anticipated effect size (Cohen *d*) of 0.5 and a desired statistical power level of 0.80. The required sample size per group was 100. The unpaired student t test and the chi-square test were used for the analysis of the variables and categorical data. Differences were considered significant at a *P* value < 0.05 .

A total of 207 patients were enrolled in the study, of which 200 were studied, as the rest did not satisfy the inclusion criteria. The patients were randomized into 2 equal groups of 100 patients based on a computer-generated random number table. The study was double-blind, the randomization table was stored centrally, and the group assigned to each patient was conveyed to the author. Patients in Group A were given tadalafil 10 mg once daily, and those in Group B received tamsulosin 0.4 mg (prolonged release capsule) once daily. In both groups, the drugs were continued until stone expulsion or for a maximum of 4 weeks. There were no sponsors for our study. The drugs were prescribed by us and bought in pharmacies by all the patients included in the study. Each enrolled patient was assessed by physical examination, serum creatinine level, urine culture, ultrasonography, and non-contrast computed tomography of the KUB region as needed. Patients were instructed to drink plenty of fluids, take one tablet of diclofenac 50 mg orally during episodes of pain, with a maximum dose of 150 mg per day, and filter their urine using a standard mesh net to detect stone expulsion. The expulsion time, analgesic use, number of hospital visits for pain, follow-up period, and adverse effects of drugs were noted. The maximum follow-up was for 4 weeks after which patients underwent semi-rigid ureterorenoscopy for removal of stones that were not expelled. The primary endpoint studied was the stone expulsion rate. Secondary endpoints studied were stone expulsion time, number of pain episodes, analgesic use, and side effects related to medical therapy. Even though a few patients passed fragments of stone during the treatment period, CT KUB was still performed in all the patients to confirm complete clearance of stones.

All the classified and categorical data were analyzed for both the groups by using the chi-square test. The 2-tailed test was used for all comparisons; the level of significance was taken as *P* < 0.05 . The data was entered into a Microsoft Excel worksheet and was analyzed using the SPSS Version 17 (SPSS Inc, Chicago, IL). There were no conflicts of interest in our study as the drugs were prescribed and bought in pharmacies by all patients included in the study.

RESULTS

Of 207 patients, 200 met the inclusion criteria, which were randomly assigned into 2 groups. There was a dropout of 2 patients in both Groups A and B, whereas the remaining patients completed the study. No statistically significant differences were observed regarding patients' age, gender, stone size, and Hounsfield units (Table 1).

The stone expulsion rate was 84.0% in Group A and 68.0% in Group B; Group A showed a significantly higher stone expulsion rate compared with Group B (P value = 0.0130). The mean time for stone expulsion in Group A was 14.7 ± 3.8 days, and in Group B was 16.8 ± 4.5 days. The time was significantly less in Group A than Group B (P value = 0.0021). Of 200 patients, stones were not expelled in 48 patients (16, 32 patients in groups A, B, respectively) even after 4 weeks of MET. These patients subsequently underwent ureteroscopic stone removal. Compared with Group B (1.3 ± 0.9), the average number of episodes of colicky pain were significantly less in Group A (0.45 ± 0.68 ; P value = .0002). Additionally, the mean requirement of analgesia was significantly less in Group A (1.88 ± 0.60) than in Group B (2.6 ± 0.8).

Drug-related adverse effects such as headache, dizziness, orthostatic hypotension, and backache were more frequent in Group B patients (P value >0.05), but not significantly enough to exclude them from the study. Abnormal ejaculation was seen in 6% of patients in Group A, and 12% in Group B, which was again not statistically significant (Table 2).

DISCUSSION

The advances in minimally invasive techniques have led to a decrease in the treatment related morbidity associated with management of ureteric calculi. These advances include shock wave lithotripsy and ureteroscopic lithotripsy. Although these approaches are less invasive than traditional open surgical methods, they are expensive and have inherent risks. Hence, observation has been advised for small ureteral stones, which have a high probability to pass spontaneously. The use of the expectant approach for distal ureteric stones can be extended with the use of adjuvant medical expulsive therapy (MET), which is able to reduce symptoms and facilitate stone expulsion.

The factors influencing expulsion of calculi include stone size, shape, and location, ureteric edema, and ureteric convolutions. Of these, the location of the calculus and its size are the most important factors.

The management of patients with ureteral calculi has changed dramatically in the current era, with

Table 1. Demographic information and results of groups

Parameter	Group A	Group B	<i>P</i> -value
Mean age (years)	36.34 \pm 11.32	37.53 \pm 12.67	0.485
No. male/female	65/35	67/33	0.881
Mean stone size (mm)	7.10 \pm 1.43	7.22 \pm 1.25	0.528
Mean Hounsfield unit (HU/mm)	59.23 \pm 1.25	58.96 \pm 1.31	0.138
Expulsion rate (%)	84.0 (84/100)	68.0 (68/100)	0.0130
Mean expulsion time (days)	14.7 \pm 3.8	16.8 \pm 4.5	0.0021
Mean analgesic use	1.88 \pm 0.60	2.6 \pm 0.8	0.0001
Mean no. colic episodes	0.45 \pm 0.68	1.3 \pm 0.9	0.0002
Mean no. hospital visits	2.10 \pm 0.90	2.4 \pm 0.8	0.014

Table 2. Adverse effects in each group

Parameter	Group A	Group B	<i>P</i> -value
Headache (%)	14	11	0.666
Dizziness (%)	12	10	0.820
Backache (%)	9	11	0.813
Orthostatic hypotension (%)	8	10	0.804
Rate of abnormal ejaculation (%)	6	12	0.230
Improvement in erectile dysfunction (%)	13	–	–

the conservative approach being the primary focus, its main benefit being minimum patient morbidity. Conservative nonsurgical approaches are usually implemented in the treatment plan of distal ureteral stones of size 5–10 mm as these are less likely to pass spontaneously [9, 10].

According to earlier studies, the expulsion rate of distal ureteric stone by watchful waiting is 25–54% with mean expulsion time >10 days and is associated with high analgesic requirement even for stones <5 mm. To improve the expulsion rate and reduce analgesic requirement, medical therapy is considered for distal ureteral stones [11, 12].

In 2005, according to Sigala et al [13], the most common adrenoreceptors found in the ureter are α -1D and α -1A. The authors also demonstrated that the distal ureter express a greater amount of α -1 adrenoreceptor messenger ribonucleic acid than the proximal and medial ureter. Therefore, studies have been conducted to determine the effect of combined α -1A and α -1D selective antagonist, tamsulosin, which revealed improved expulsion rate of medium-sized (5–10 mm) stones. We observed an expulsion rate of 68.0% with tamsulosin, which is better than historical controls used in earlier studies with rates of 43% and 30.2% [14, 15]. Thus, tamsulosin represents a non-invasive and cost-effective alternative to interventional approaches. Our results however

do not match with those of the SUSPEND Trial [16] which is a multicentre, randomized, placebo controlled trial and concludes against the use of tamsulosin as a MET for patients with ureteric calculus. The reason for which can be explained as follows:

Stone location

Our study in comparison consist of patients with stones located in the lower ureter whereas the SUSPEND Trial [16] consists of patients with a stone anywhere in the ureter, including the upper, middle or lower ureter. MET is best suited for stones in the lower ureter as this part of the ureter is lined by α -1 adrenergic receptors, particularly the subtype α -1D, which are more populated in its distal third, and play an important role in the lower ureteric physiology through an effect on detrusor and ureteric smooth muscle contraction. The blocking of these receptors subsequently induces selective relaxation of the ureteric smooth muscle, which will result in ureteric lumen dilatation facilitating antegrade stone propagation. Hence, the results of both the studies cannot be compared on the same scale.

Stone size

As per the SUSPEND Trial [16], approximately 75% of patients in each group are patients with a stone size of less than 5 mm and according to the European Association of Urology Guidelines (2015) on Urolithiasis, there exists a high likelihood of spontaneous passage of stones up to ~5 mm, hence MET is less likely to increase the stone-free rate. Therefore the results cannot be considered as a conclusion against MET and also cannot be compared with our study as our study consist of patients with stone size 5 to 10 mm.

Stone clearance

Spontaneous stone passage in the SUSPEND Trial [16] was defined by the absence of need for intervention to assist stone passage at 4 weeks; investigations were not performed to confirm the findings. Whereas in our study, in addition to patients presenting their passed stone fragments, stone passage was confirmed by CT KUB.

Assessment

Assessment of stone clearance was based on symptoms in the SUSPEND Trial [16]. At no point in the study were periodic radiological investigations performed in order to confirm stone clearance hence some patients might have had asymptomatic stones. Whereas in our trial stone clearance was confirmed with CT KUB.

We decided to use tadalafil based on reports by Gratzke et al. [17] who demonstrated the role of phosphodiesterase inhibitors in relaxation of ureteric muscles in the sequence of vardenafil > sildenafil > tadalafil [18, 19]. As tadalafil is more selective compared with sildenafil for PDE-5 than phosphodiesterase-6 receptors, which are present in the retina, visual problems are less likely. Tadalafil has the longest duration of action (~36 hours and a half life of 17.5 hours) among the current PDE-5 inhibitors, and its activity is unaffected by meals [20, 21]. To keep adverse effects at a minimum, we used tadalafil in smaller doses (10 mg). Another reason to choose tadalafil at low doses was because studies by Santosh et al. [21] and Jayant et al. [22], demonstrated that combination of tadalafil with tamsulosin has significant role in ureteric stone expulsion, without showing any adverse hemodynamic changes [17, 20].

With regard to the primary endpoint, both the compared groups in our study proved superior with the historical controls of watchful waiting. In this study, we did not use a placebo or control group because our objective was to compare prospectively the efficacy of these two groups of drugs that can potentially modulate ureteral motility. Also in the past, trials have been carried out comparing various drugs with placebo for medical expulsive therapy and results have shown that drugs are superior to placebo, hence we decided to exclude placebo and compare the efficacy of already proven tamsulosin with the newer drug tadalafil for medical expulsive therapy. We observed an apparently higher expulsion rate and lower expulsion time in the tadalafil group than in the tamsulosin group, which was statistically significant (84%; 14.7 \pm 3.8 days *vs.* 68%; 16.8 \pm 4.5 days; *P* value = .0130, *P* value = 0.0021).

It is important to note that the drug given to Group B acts on α -1 adrenoceptors, whereas the drug in Group A acts through PDE receptors, which are totally separate pathways in modulation of ureteric motility and thus opening the potential of combining these drugs to further aid the ureteric stone expulsion. A combination of tamsulosin and tadalafil has already been successfully used by Jayant et al. [22]. Kumar et al. showed a stone expulsion rate of 66.7% with tadalafil in comparison to 64.4% with tamsulosin [23].

The reported side effects were mild to moderate and were well tolerated in our study, probably because of the younger study population and the lack of any associated comorbidity. However, abnormal ejaculation was observed in 6% of patients in Group A, and in 12% of patients in Group B, but was not statistically significant (*P* value = 0.230).

The results we obtained were statistically significant although further studies on MET are needed to de-

termine the superiority of tadalafil over tamsulosin and the potential use of this drug with tamsulosin.

CONCLUSIONS

The results of this study indicate that tadalafil significantly increases ureteric stone expulsion and simultaneously provides better pain control and

significantly lowers analgesic requirement. Both α -1 adrenoreceptor antagonists and PDE-5 inhibitors act through different pathways, hence opening up the potential of using these two drugs together as combined therapy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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