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Comparing tamsulosin, silodosin versus silodosin plus tadalafil as medical expulsive therapy for lower ureteric stones: A randomised trial

Md Jawaid Rahman, M. Shazib Faridi *, Naloh Mibang, Rajendra Sinam Singh

Department of Urology, Regional Institute of Medical Sciences, Imphal, Manipur, India

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KEYWORDS

Efficacy;
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ABBREVIATIONS

AR, adrenergic receptor;
cGMP, cyclic guanosine monophosphate;
KUB, kidney, ureter, and bladder;
MET, medical expulsive therapy;
PDE(-5), phosphodiesterase (type 5);
USG, ultrasonography

Abstract ***Objective:*** To compare the efficacy of tamsulosin, silodosin, and silodosin plus tadalafil as medical expulsive therapy (MET) for distal ureteric calculi.

Methods: In all, 120 patients who met the inclusion criteria were randomised into one of three treatment arms: tamsulosin (Group A), silodosin (Group B), and silodosin plus tadalafil (Group C). The drugs were given for a maximum of 4 weeks. The primary endpoint was the stone expulsion rate and secondary endpoints were stone expulsion time, number of pain episodes, and side-effects associated with MET. The follow-up period was for 4 weeks, after which ureteroscopic lithotripsy was done to remove any stones that were not expelled.

Results: There was a statistically significantly higher stone expulsion rate in Group C (90%) as compared to groups A (57.5%) and B (77.5%) with a shorter mean time to stone expulsion. Also, there were statistically fewer pain episodes in Group C as compared to groups A and B. There were no serious side-effects.

Conclusion: The present study concludes that the combination of silodosin and tadalafil increases the ureteric stone expulsion rate and decreases the expulsion time significantly. This combination provided significantly better control of pain without any serious side-effects.

Introduction

Urolithiasis is one of the most common urological diseases and affects 5–10% of people globally [1]. In all, 20% of all urinary tract stones are ureteric in location, and ~70% are found in the lower one-third of the ureter

* Corresponding author.
E-mail address: drshazibfaridi@gmail.com (M.S. Faridi).

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[2]. There has been a steep rise in minimally invasive procedures [3] but medical expulsive therapy (MET) is still regarded as an established treatment option for the management of distal ureteric stones. Stone location, size, number, ureteric spasm, mucosal oedema or inflammation, and ureteric anatomy are the factors affecting passage of ureteric stones [4]. Reported spontaneous passage rates for distal ureteric stones of < 5 mm range from 71% to 98% and for stones measuring 5–10 mm from 25% to 53% [5]. Even though the stones pass in most cases, they can cause acute pain to the patient whilst passing down the ureter. So, there is a further need for agents that promote better stone passage with reduced need for surgical interventions.

In MET, passage of the stone is facilitated by relaxation of ureteric smooth muscle, a decrease in the ureteric mucosal oedema, and an increase in the hydrostatic pressure proximal to the stone. There are abundant α_1-adrenergic receptors (ARs) in the distal third of ureteric smooth muscle. These receptors when blocked inhibit basal smooth muscle tone and hyperperistaltic uncoordinated frequency, whilst maintaining tonic propulsive contractions [6]. Ureteric spasms due to stones interfere with calculi expulsion. Thus, tamsulosin an α_1-adrenergic receptor blocker causes ureteric muscle relaxation with maintenance of normal antegrade peristaltic activity that facilitates the passage of stones [2].

Phosphodiesterases (PDEs) regulate intracellular cyclic nucleotide turnover influencing smooth muscle tension. PDE-5 inhibitors, such as sildenafil or tadalafil, act via the nitric oxide/cyclic guanosine monophosphate (cGMP)-signalling pathway, resulting in increased levels of cGMP, which leads to ureteric smooth muscle relaxation [7]. The AUA as well as the European Urological Association ureteric stones clinical guidelines support the use of MET for patients with distal ureteral calculi of < 10 mm. In comparison with surgical intervention for ureteric stones, MET has a high safety profile and low cost [8].

Silodosin is a more selective α_{1A}-adrenergic receptor antagonist than tamsulosin and has a better stone expulsion rate than tamsulosin [9]. Tadalafil, a PDE-5 inhibitor used alone or combined with tamsulosin is safe, efficacious, and well tolerated for the treatment of lower ureteric stones [10]. Tadalafil was used in place of sildenafil as it is associated with less visual problems and as its absorption does not appear to be affected by meals [11].

The combination of silodosin and tadalafil has greater potency than either drug alone for the treatment of LUTS associated with BPH [12], but no study has been reported using these two drugs in combination for the treatment of lower ureteric stones.

Therefore, we decided to perform a prospective randomised study to evaluate the role of combined silodosin and tadalafil in comparison with proven silodosin and tamsulosin individually for ureteric stone expulsion.

Patients and methods

This was a prospective study conducted at a tertiary care centre in the north eastern part of India. It was conducted from August 2014 to July 2015 after obtaining Institutional Ethics Committee clearance. Inclusion criteria were: Patients aged $\geq$18 years with a distal ureteric stone of 5–10 mm in greatest dimension diagnosed by full bladder ultrasonography (USG) of the kidney, ureter, and bladder (KUB) or X-ray KUB; if patient's pain subsided in 1 day with 75 mg diclofenac (i.m.); and the patient was prepared to enrol in the study. Exclusion criteria were: UTI, severe hydroureteronephrosis, multiple ureteric stones, solitary kidney, renal insufficiency, previous therapies for the stone, history of open surgery/endoscopic interventions, concomitant treatment with calcium antagonists, β-blockers, corticosteroids or nitrates; ureteric strictures, pregnant or lactating mothers, and those who refused to enrol in the study.

In all, 135 patients were enrolled in the study, of which 120 patients met the inclusion criteria. After providing written and informed consent, patients were randomised into three equal groups based on computer generated random number table. Group A was given tamsulosin 0.4 mg once daily, those in Group B were given silodosin 8 mg once daily, and those in Group C were given a combination of silodosin 8 mg with tadalafil 5 mg once daily (Fig. 1). In all the groups, drugs were continued until stone expulsion or for a maximum period of 4 weeks. All patients were assessed by physical examination, serum creatinine levels, urine culture, and USG KUB or X-ray KUB when required. Along with the allocated drug, patients were advised to take plenty of fluids and tablet diclofenac 50 mg orally during pain episodes. Patients were followed-up for 4 weeks, after which ureteroscopic lithotripsy was used to remove any stones that had not been expelled. The primary endpoint was the stone expulsion rate and secondary endpoints were stone expulsion time, rates of interventions such as ureterorenoscopy, number of pain episodes, and side-effects associated with MET. The stone expulsion time was defined as the number of days from the random allocation to the expulsion of stone and expulsion of stone was confirmed by USG KUB or X-ray KUB.

Comparison of all three groups for normally distributed data was performed using ANOVA. Group wise comparison of data was done by z-score. A $P < 0.05$ was considered to be statistically significant and the power used was 0.80. The required sample size per group was 40. The Statistical Package for the Social

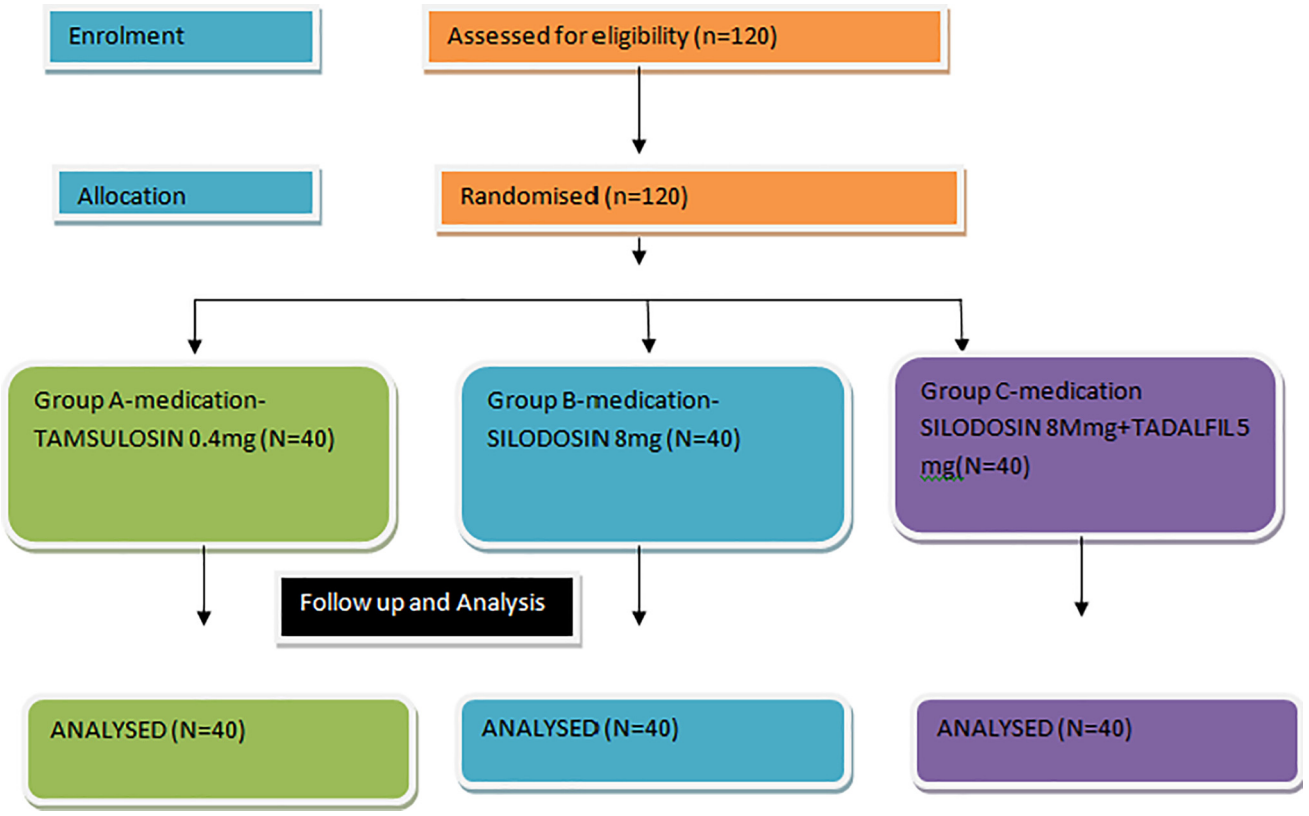

Fig. 1 Flowchart of study design.

Sciences (SPSS® version 21; SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

Of 135 patients, 120 patients were included. There was no statistically significant difference between the groups for patient's age, gender, body mass index, or stone size (Table 1).

Stone expulsion occurred in 23 of 40 patients (57.5%) in Group A, in 31 of 40 patients (77.5%) in Group B, and 36 of 40 patients (90%) in Group C. Group C showed a significantly higher stone expulsion rate as compared to groups A and B ($P = 0.004$ and $P = 0.05$, respectively). Group B also had a statistically significant higher stone expulsion rate as compared to Group A ($P = 0.04$). The mean (SD) expulsion time in Group A was 21 (4.6) days, in Group B was 15 (3.3) days, and in Group C was 12 (2.2) days. The time was significantly less in Group C than Group A ($P < 0.001$) and B ($P < 0.001$). Also, the expulsion time between Group A and B was also significantly less ($P < 0.001$) (Table 2).

In 30 patients, the stone was not expelled even after 4 weeks of MET (17, nine and four patients in Groups A, B and C, respectively). These patients were subsequently treated with ureteroscopic lithotripsy.

The mean (SD) pain episodes were less in Group C [0.6 (0.2)] as compared to Group A [1.6 (1.1); $P < 0.001$] and Group B [0.8 (0.06); $P < 0.001$]; compared with Group A, Group B had fewer pain episodes ($P < 0.001$) (Table 2).

Table 1 Demographic profile of study patients.

Variable	Group A Tamsulosin	Group B Silodosin	Group C Silodosin + tadalafil	*P*
Male/female, *n*	24/16	22/18	25/15	0.84
Mean (SD)				
Age, years	38 (10)	34 (12)	35 (10)	0.22
Body mass index, kg/m^2	26.33 (2.20)	26.99 (2.93)	26.15 (2.5)	0.30
Stone size, mm	7.5 (1.20)	7.4 (1.30)	7.6 (1.35)	0.78

Table 2 Treatment outcomes.

Variable	Group A Tamsulosin	Group B Silodosin	Group C Silodosin + tadalafil	*P*		
				A vs B	A vs C	B vs C
Expulsion rate, % (*n*/*N*)	57.5(23/40)	77.5(31/40)	90(36/40)	0.04	0.004	0.05
Mean (SD)						
Expulsion time, days	21 (4.6)	15 (3.3)	12 (2.2)	<0.001	<0.001	<0.001
Pain episodes, *n*	1.6 (1.1)	0.8 (0.06)	0.6 (0.2)	<0.001	<0.001	<0.001
Side-effects, %						
Headache	10	12.5	15	0.726	0.477	0.322
Dizziness	10	7.5	10	0.689	–	0.689
Backache	5	7.5	10	0.642	0.389	0.689
Orthostatic hypotension	7.5	5	7.5	0.064	–	0.064
Retrograde ejaculation*	12.5	15	15	0.322	0.322	–

* In males.

Drug-associated adverse effects such as headache and backache were reported more in Group C but this was not statistically significant ($P > 0.05$). Moreover, adverse effects, such as dizziness and orthostatic hypotension were similar in groups A and C and more than in Group B, but this difference was not statistically significant ($P > 0.05$). In males, retrograde ejaculation was reported in 12.5% in Group A and 15% in both groups B and C but it was again statistically non-significant (Table 2).

Discussion

Different treatment methods for distal ureteric stones are available ranging from open surgery to minimally invasive methods. But, all these approaches are associated with complications. So, there has been a paradigm shift in the treatment of distal ureteric stone with a primary focus on MET.

According to the available literature, spontaneous passage of distal ureteric stone using a conservative approach for stones of 5–10 mm is less likely [13], with a mean expulsion time of >10 days [14].

In 1970, Malin et al. [6] described the role of ARs in the human ureter. The α-ARs were distributed in the human distal ureter as follows: $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$. The stimulation of α_1-ARs in the ureter increases the force of contraction and the frequency of peristalsis. Blockade of α_1-ARs inhibits basal tone, reduces the peristalsis and frequency, and decreases the intraluminal pressure whilst maintaining the rate of fluid transport and hence increases the chances of stone expulsion [15].

Tamsulosin, which is a combined α_{1D}- and α_{1A}-AR blocker increases stone expulsion rates, decreases pain, and reduces mean time to stone expulsion when compared to placebo [2,15]. Silodosin is highly selective α_{1A}-AR antagonist and it has a better stone expulsion rate and stone expulsion time as compared to tamsulosin [9]. Sildenafil and tadalafil, PDE-5 inhibitors, act via the nitric oxide/cGMP-signalling pathway, which results in increased levels of cGMP, leading to ureteric smooth muscle relaxation, which helps in stone passage [10,16]. To the best of our knowledge, the present study is the first randomised, controlled, clinical trial to compare the efficacy of tamsulosin, silodosin, and silodosin combined with tadalafil.

In the present study, there was a significantly better expulsion rate and lower mean expulsion time in Group B [77.5%; mean (SD) 15 (3.3) days] as compared to Group A [57.5%; mean (SD) 21 (4.6) days] ($P = 0.04$ and $P < 0.001$, respectively). The possible explanation could be due to highly selective α_{1A}-AR antagonist action of silodosin when compared with α_1-AR antagonist action of tamsulosin.

Jayant et al. [17] reported that a combination of tadalafil with tamsulosin had better outcomes in ureteric stone expulsion. In their study, the stone expulsion rate was 83.6% ($P = 0.031$). In our present study, Group C had a statistically significantly higher stone expulsion rate (90%) as compared to groups A and B ($P = 0.004$ and $P = 0.05$, respectively).

The reason for a better expulsion rate in Group C may be due to the combination of two drugs with different mechanism of action. Drug A and drug B both act on α_1-ARs, whereas drug C acts via PDE-5 inhibition, which are totally different pathways in the modulation of ureteric motility and thus may have the potential of combining these drugs to further help in ureteric stone expulsion.

The mean (SD) expulsion time in Group C was also significantly less [12 (2.2) days]) as compared to Group A [21 (4.6) days; $P < 0.001$] and Group B [15 (3.3) days; $P < 0.001$]. In the Jayant et al. study [17], the mean (SD) expulsion time was 14.9 (4.4) days with the tadalafil and tamsulosin combination compared to 16.7 (4.8) days for tamsulosin alone ($P = 0.003$).

Ureteric colic occurs due to an increase in intraureteric pressure proximal to site of obstruction. α-AR antagonists block C fibres responsible for mediating ureteric colic [18]. In our present study, Group C had significantly fewer pain episodes than Group A and Group B ($P < 0.001$), and Jayant et al. [17] also showed

significantly fewer pain episodes with a tadalafil and tamsulosin combination as compared to tamsulosin alone. This may be due to two drugs with different actions on the ureter. Silodosin blocks the C fibres and tadalafil probably decreases the frequency and amplitude of ureteric phasic peristaltic contractions that accompanies ureteric obstruction and decreases the intraureteric pressure, and hence decreases pain episodes.

No serious side-effects were encountered in the present study, which may be due to the young study population without any associated co-morbidities. However, retrograde ejaculation was least in Group A but was not statistically significant, when comparing all three groups with each other.

A limitation of the present study is that CT KUB was not done to assess the ureteric stone because of financial constraints. Moreover, combination of drugs increases the cost of treatment.

Conclusion

The present study concludes that the combination of silodosin and tadalafil increases the ureteric stone expulsion rate and decreases the expulsion time significantly. This combination provides significantly better control of pain without any serious side-effects. Further studies are required on large sample size.

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None.

Conflict of interest

None.

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