DOI: 10.7860/JCDR/2023/62238.18492

Original Article

Others Section

Comparison of Synergistic Action of Alpha Blockers and Tadalafil in the Management of Lower Ureteric Stones as Medical Expulsive Therapy: A Prospective Cohort Study

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ABSTRACT

Introduction: Medical Expulsive Therapy (MET) involves the utilisation of different drugs that act on the ureter through various mechanisms. Alpha-1 adrenoceptor and Phosphodiesterase (PDE) regulate ureteric motility thus combination of these drugs can increase the ureteric stone expulsion rate by complementing each other's actions.

Aim: To assess the synergistic role of alpha-blocker and Tadalafil therapy in facilitating the spontaneous expulsion of distal ureteral stones.

Materials and Methods: A prospective cohort study was conducted in the Department of Urology at a Tertiary Care Centre (NSCB Medical College) from April 2020 to January 2022. A total of 281 patients diagnosed with lower ureteric stones (5-10 mm) were divided into five study groups: Group A was treated with tamsulosin, group B with silodosin, group C with tadalafil alone, group D with tamsulosin and tadalafil, and group E treated with a combination of silodosin and tadalafil. Corticosteroid (deflazacort 6 mg) was also included in every group. All patients were reassessed after three weeks of treatment for stone expulsion rate, expulsion time, the number of hospital visits for pain, and adverse effects of drugs. The statistical data was analysed using Statistical Package for Social Sciences (SPSS) software (version 21.0, IBM Corp, USA). The Chi-square test and Analysis of Variance (ANOVA) test were used to determine the effect on stone expulsion rate and expulsion time. The confidence interval was 95%, and the significance level of the p-value was set <0.05.

Results: The stone expulsion rates in group A, B, C, D, and E were 70.91%, 79.63%, 52.63%, 84.21%, and 86.20%, respectively, which was significant (p=0.00194). The mean time taken for stone expulsion in group A, B, C, D, and E were 8.95±1.73, 8.43±1.57, 9.86±1.90, 7.96±2.03, and 7.75±1.84 days (p=0.0001). Minor side effects were not significant, except for retrograde ejaculation in group B and E, and 22.8% of patients needed hospitalisation in group C (tadalafil alone).

Conclusion: Combination therapy is safe, efficacious, and well-tolerated as MET for distal ureteric calculi in the 5-10 mm range, thereby avoiding surgical procedures and providing faster relief for the patients.

Keywords: Combination therapy, Expulsion time, Silodosin, Stone expulsion rate, Ureteric calculi

INTRODUCTION

Urolithiasis is a disease of public health importance and economic consequence as it involves all ages and has a high recurrence rate of approximately 50% within five years and 75% at 10 years [1]. Overall, ureteric stones constitute only 20% of urolithiasis, but symptom-wise, they are most problematic. The spontaneous passage rate for distal ureteral stones is 70% to 98% for sizes < 5 mm and 25% to 50% for sizes 5-10 mm [2]. This rate is influenced by multiple factors such as stone location, number, size, composition, ureteral spasm, mucosal inflammation or oedema, and ureteral anatomy. The use of MET for stone expulsion is acceptable to reduce ureteral oedema and spasm, thereby relaxing the smooth muscles [3].

Ureteral calculi of any size result in renal obstruction, and for preventing irreversible renal damage, the management of the calculi is imperative. The mechanism behind the colicky pain in ureteric stone is an increase in the intraluminal pressure above the site of obstruction. This pain is mediated by C fibres, and α-blockade may palliate the ureteric colic by blocking this pathway [4]. MET has now become an accepted method of treatment, which involves the utilisation of different drugs acting on the ureter by various mechanisms. The ureter is rich in α1-adrenergic receptors, especially the subtype α1D, which are more abundant in its lower third, and they play a major role in ureteric smooth muscle contraction [5]. The use of a selective α-adrenoceptor blocker for MET is recommended by both the American Urological Association (AUA) and the European Association of Urology (EAU) [6,7].

The PDE Inhibitors (PDEIs) also have an action on ureteric motility; thus, the combination of these drugs may increase the ureteric stone expulsion rate. Various studies have used a combination of tamsulosin and tadalafil with a higher expulsion rate and a shorter time to expulsion compared to tamsulosin alone, along with the possibilities of combining silodosin with tadalafil [8,9]. Drugs such as steroids, calcium antagonists, and glyceryl trinitrate inhibit the basal tone of the ureters, their peristaltic frequency, ureteral contractions, and ureteral spasm, thus favouring stone expulsion [10]. Despite these studies, many urologists across the globe don't use the tadalafil and α-blocker combination with no specific reason; it may be just inherent clinical practice culture. The present study has used these combinations to elaborate on the clinical benefits of their use in assisting in the medical expulsion of stones. Hence, the present study attempted to assess the role of combined α-blocker and tadalafil therapy in facilitating the spontaneous expulsion of distal ureteral stones.

MATERIALS AND METHODS

A prospective cohort study was conducted in the Department of Urology at a Tertiary Care Centre (NSCB Medical College) in the Department of Urology from April 2020 to January 2022. Institutional Ethics Committee approval was obtained for the study. A detailed informed consent was obtained from all patients before their enrollment in the study.

Inclusion criteria: Patients diagnosed with lower ureteric stones in the size range of 5-10 mm and aged over 18 years were included in the study.

Exclusion criteria: Patients with ureteric stones and active infection, severe/refractory pain, severe hydronephrosis, acute or chronic renal failure, any major co-morbidity, or calculi elsewhere in the urinary tract were excluded from the study.

Sample size calculation: The sample size was determined based on the prevalence of ureteric calculi using the Cochran formula (Cochran, 1977) [11]. A total of 293 patients diagnosed with lower ureteric stones (5-10 mm) were enrolled in the study. However, 12 patients were lost to follow-up and were subsequently removed, resulting in a final sample size of 281 patients.

Study Procedure

Initially, all patients were evaluated on an outpatient basis following the standard protocol, which included urine routine and microscopy, urine culture and sensitivity (whenever required), complete blood count, renal function test, and abdominal ultrasonography. Diagnosis was confirmed by Non-contrast Computed Tomography (NCCT). After the diagnosis, all eligible patients were divided into five study groups using a simple randomisation technique. Each group was treated with medication for a duration of three weeks. Group A received tamsulosin 0.4 mg, group B with silodosin 8 mg, group C with tadalafil 10 mg alone, group D received tamsulosin 0.4 mg and tadalafil 10 mg, and group E received silodosin 8 mg and tadalafil 10 mg. Corticosteroid (deflazacort 6 mg) was also included in every group for seven days. Patients were also provided with paracetamol, tramadol, and diclofenac as needed.

All patients were carefully followed-up, monitoring their clinical symptoms through X-ray and ultrasound weekly. After three weeks, reassessment was done using NCCT to check the clearance rate of stones, and the findings were noted. The results of the five groups were compared based on patient characteristics, stone expulsion rate, stone expulsion time, and side effects of the drugs. The stone expulsion rate was assessed by calculating the percentage of patients with expelled stones out of the total number of patients included in that particular group. Patients were monitored for symptoms and radiologically with X-rays and ultrasound to assess expulsion and correlate it with the duration of medications administered. The number of days taken for the stone to pass after beginning of MET was taken to be the stone expulsion time.

Patients who experienced treatment failure in each group after the three weeks of follow-up were successfully treated with ureteroscopy. The primary outcomes of the present study were the stone expulsion rate and stone expulsion time (in days). The secondary outcomes included pain episodes, abnormal ejaculation, and other complications.

STATISTICAL ANALYSIS

The SPSS software (version 21.0, IBM Corp, USA) was used for analysis. The Chi-square test was used to determine differences between categorical variables, and the ANOVA test was used to determine significant differences in independent variables between the groups. The confidence interval was set at 95%, and the significance level of the p-value was set <0.05.

RESULTS

A total of 281 patients were studied in different groups. The mean age in groups A, B, C, D, and E as shown in [Table/Fig-1]. There was no significant relation between age and stone expulsion. Additionally, no significant difference in mean stone size was found in any of the groups between patients who were stone-free and those who were not. The mean calculus size in group A was 5.93±2.12 mm, in group B it was 6.17±2.03 mm, in group C it was 5.97±2.31 mm, in group D it was 5.84±2.43 mm, and in group E it was 5.89±1.99 mm. The p-value was 0.9458, which was not significant. The side variation (i.e., left vs right) in all five groups did not affect the study results, as shown in [Table/Fig-1].

Variables	A (n=55)	B (n=54)	C (n=57)	D (n=57)	E (n=58)	p-value
Age (in years) (mean±SD)	38.46± 10.68	37.87± 9.62	34.94± 7.07	35.72± 7.93	36.76± 8.73	0.1993*
Male and female (ratio)	32/23	30/24	36/21	31/26	36/22	0.8437#
BMI (kg/m^2)	23.42± 1.4	23.56± 2.2	22.97± 1.9	23.72± 2.1	23.67± 1.7	0.2135*
Stone size (mm) (mean, SD)	5.93± 2.12	6.17± 2.03	5.97± 2.31	5.84± 2.43	5.89± 1.99	0.9458*
Right and left	31/24	21/33	25/32	32/25	30/28	0.3077#

[Table/Fig-1]: Patients characteristics.
*ANOVA; #Chi-square; BMI: Body mass index

There was no statistically significant difference between the five groups in terms of age, gender, BMI, size, and laterality of the calculus. The stone expulsion rates for groups A, B, C, D, and E were 70.91%, 79.63%, 52.63%, 84.21%, and 86.20%, respectively. The p-value was 0.00194, indicating a highly significant difference, as shown in [Table/Fig-2].

Expulsion	Group A (n=55)	Group B (n=54)	Group C (n=57)	Group D (n=57)	Group E (n=58)	p-value
Yes	39	43	30	48	50	0.00194*
No	16	11	27	9	8	
Rate (%)	70.91	79.63	52.63	84.21	86.20	

[Table/Fig-2]: Expulsion rate.
Test applied: Chi-square, *p-value <0.05, χ^2=16.7339, HS

When comparing the various groups, groups A, B, D, and E required significantly less analgesic than group C (10% vs 37%; p-value 0.003). The comparison of expulsion rates between the groups showed that the p-value was significant in B vs C, C vs D, and C vs E, indicating that silodosin and various combinations performed better than tadalafil alone, as shown in [Table/Fig-3].

Comparison between groups	χ^2	p-value
A vs B	1.112	0.291655
A vs C	3.9534	0.46776
A vs D	2.8562	0.91021
A vs E	3.9494	0.46889
B vs C	8.9774	0.002733*
B vs D	0.3939	0.53024
B vs E	0.8588	0.354074
C vs D	13.1538	0.0027*
C vs E	15.0367	0.0091*
D vs E	0.091	0.762972

[Table/Fig-3]: Comparison of expulsion rate between the groups.
#Chi-square, Confidence interval was 95% and *significant p-value <0.05

The mean time taken for stone expulsion in groups A, B, C, D, and E was 8.95, 8.43, 9.86, 7.96, and 7.75 days, respectively. The p-value was 0.0001 (<0.05), indicating a highly significant difference, as shown in [Table/Fig-4]. The intergroup comparison of expulsion time, and significant differences were observed between groups A vs E, B vs C, C vs D, and C vs E [Table/Fig-5].

All five groups of patients experienced minor side effects associated with expulsive therapy. However, none of these led to treatment discontinuation. In group A, two patients experienced sudden transient hypotension, and one had dizziness. In group B, two patients had transient hypotension, and three experienced headache and vomiting for two days, which was relieved with ondansetron. In group C, there were two cases of malaise and two cases of diarrhoea. The incidence of retrograde ejaculation was considerably

high in group B and E (six male patients in group B and seven patients in group E), as shown in [Table/Fig-6].

Explulsion	Groups	n	Yes	Mean time of stone expulsion (days)	Standard deviation	p-value
Yes	A	55	39	8.95	1.73	p=0.00001*
	B	54	43	8.43	1.57	
	C	57	30	9.86	1.90	
	D	57	48	7.96	2.03	
	E	58	50	7.75	1.84	
Total		281	210			

[Table/Fig-4]: Expulsion time.
*ANOVA test, *significant p-value <0.05; N is total number of patients in each group

Group comparison	Diff=	95% CI	p-value
A vs B	0.5200	0.4792 to 0.4392	0.5710
A vs C	0.9100	0.0364 to 1.8564	0.6600
A vs D	0.9900	-1.9364 to -0.0436	0.3530
A vs E	1.2000	-2.1424 to -0.2576	0.00490*
B vs C	1.4300	0.4791 to 2.3809	0.0005*
B vs D	0.4700	-1.4209 to 0.4809	0.6557
B vs E	0.6800	-1.6269 to 0.2669	0.2827
C vs D	1.9000	-2.8379 to -0.9621	0.001*
C vs E	2.1100	-3.0439 to -1.1761	0.001*
D vs E	0.2100	-1.1439 to 0.7239	0.9722

[Table/Fig-5]: Comparison of expulsion time between the groups.
Tukey's HSD post-hoc test, *significant p-value <0.05; CI: Confidence interval

Side-effect	A (n=55)	B (n=54)	C (n=57)	D (n=57)	E (n=58)	Chi-square	p-value
Dizziness	1	5	1	1	2	5.9998	0.199165
Orthostatic hypotension	2	2	1	2	1	0.8225	0.935407
Retrograde ejaculation	2	6	1	2	7	7.5199	0.1108378
Intolerable pain (needed hospitalisation)	4	2	13	2	2	16.4618	0.002458*
Headache	4	3	1	2	3	2.0545	0.725727

[Table/Fig-6]: Side-effects in various groups.
Test applied: Chi-square, *p-value <0.05

These findings demonstrate that tamsulosin and silodosin cause low blood pressure, silodosin is associated with retrograde ejaculation, while intolerable pain episodes were mostly observed in patients receiving tadalafil therapy. In group C, 22.8% of the patients (13 out of 57) had to be admitted to the hospital for recurrent colic. Among them, six patients underwent DJ stenting for persistent pain. Two patients each from groups A and B were admitted for observation (3.4% and 3.7%, respectively), and none of them required ureteral stenting during this period.

DISCUSSION

The MET has now become a standard method of treatment, involving the utilisation of different drugs acting on the ureter through various mechanisms. The principle behind this approach is that administering these drugs together may have a synergistic effect, increasing their effectiveness. The present study aimed to assess the role of alpha-blocker and tadalafil combination therapy in facilitating spontaneous expulsion of distal ureteral stones. The results showed better stone expulsion rates and expulsion times without an increase in the side-effect profile.

Sigala S et al., reported that the most frequent adrenoceptors in the ureter are alpha-1A and alpha-1D [12]. Tamsulosin, an alpha-1A-selective alpha-blocker, has shown improved expulsion rates for medium-sized stones (3-10 mm). Kaneko T et al., in their study, showed stone expulsion rates of 77% in the tamsulosin group and 50% in the control arm [13]. Silodosin, with its selectivity for alpha A1 receptor being 17-fold greater than that of tamsulosin (162 vs 9.5), has been found to be better than tamsulosin in stone expulsion (82% and 58% respectively) [14]. The present study supports the action of silodosin. Corticosteroids, when combined with alpha-blockers, decrease local oedema and aid in stone expulsion. Stone expulsion rates varying from 37.5% with corticosteroids alone to 84.8% in combination with alpha-blockers have been seen in some studies [15-17]. Present study used corticosteroids in each group and found excellent results. PDE5 inhibitors, like tadalafil, act by increasing levels of cGMP, leading to ureteric smooth muscle relaxation [17]. Tadalafil, being more selective compared to sildenafil, has a long duration of action (36h) and a half-life of 17.5h, unaffected by meals [17]. Kloner RA et al., and Kloner RA found the combination of tamsulosin and tadalafil to be safe [18,19].

The present study is unique in that it assessed the efficacy of different classes of drugs individually and their combination in managing lower ureteric stones. Kumar S et al., in a randomised study on MET for lower ureteral stones, compared the efficacy of three drugs: tamsulosin, tadalafil, and silodosin [5]. The expulsion rates were 64.4%, 66.7%, and 83.3%, respectively. The rates were not significantly different between the tamsulosin and tadalafil groups. However, the present study found a significant difference in the expulsion rates of silodosin and tadalafil, which may be attributed to the different actions of the drugs and the inherent potency of silodosin. Jayant K et al., compared tamsulosin with the combination of tamsulosin and tadalafil and found a significantly reduced expulsion time, fewer colicky pain episodes, and less analgesic use [8]. Hasan HF et al., found a significantly lower pain score and a significantly lower analgesic requirement in the tadalafil group than in the placebo group [20]. The number of pain episodes and the requirement for analgesia were significantly lower for silodosin compared to tamsulosin [5]. Silodosin blocks the C fibres, and tadalafil probably reduces the amplitude and frequency of ureteric phasic peristaltic contractions, leading to a decrease in pain episodes most effectively through this combination. Many studies have evaluated the effects of silodosin as a better substitutional congener for MET. Itoh Y et al., concluded that silodosin offers tremendous potential for MET of distal ureteral stones [21]. Wang CJ et al., found a mean expulsion time of 6.31±2.13 days for silodosin with reduced analgesic consumption [22]. The findings of the present study support similar results as the above-mentioned studies.

Several studies have compared tamsulosin and silodosin. The meta-analysis conducted by Ozsoy M et al., and Hsu YP et al., found that silodosin had higher stone expulsion rates and faster expulsion times compared to tamsulosin [23,24]. Dell'Atti L, in his study, found a significantly higher expulsion rate with silodosin compared to tamsulosin (80.3% vs 61.2%) [25]. The present study concurs with these results, as it also found considerably better results with silodosin. Yuceturk CN et al., assessed the necessary dose for medical expulsion with silodosin and concluded that spontaneous stone passage was sub-optimal with 4 mg/day (50.9% vs 73.8%) compared to 8 mg/day. Present study used 8 mg/day, similar to the study by Yuceturk CN et al., [26].

Huang W et al., revealed that the expulsion rate in patients with distal ureteric stones treated with silodosin was 83.5% with a mean expulsion time of 11 days, which was superior to tamsulosin (66.9%, 14 days) and resulted in a considerable decrease in pain episodes [27]. The present study found an expulsion rate of 87.87% in combination therapy with silodosin and tadalafil, which was more than any other group, thus proving that the synergistic action of these two drugs helps in medical expulsion therapy. Studies by Alizadeh M and Magsudi M and Mettzer AC et al., observed opposite results

with silodosin, showing a reduction in expulsion time, reduced pain, and decreased need for analgesics, but no significant difference in the stone passage rate compared to placebo [28,29]. Arda E et al., also found no statistically significant superiority between tamsulosin and silodosin [30].

A prospective randomised study by Hari Bahadur KC et al., observed that the stone expulsion rate was significantly higher in the tadalafil group than in the tamsulosin group (84.1% vs 61.0%), although the side effects were more common with tadalafil, this difference was not significant [31]. Celik S et al., found that tadalafil had a higher expulsion rate than the other groups for mid-proximal ureteral stones [32]. Kumar S et al., evaluated the use of tadalafil in combination with tamsulosin and corticosteroid therapy and found that the stone expulsion rates were increased and the time to expulsion was decreased in the combination arm [33]. In the present study, the stone passage rate in tamsulosin plus tadalafil was comparable to that of Jayant K et al., (83%), but lower than that of Rahman MJ et al., (90%) [8,34]. Tamsulosin and tadalafil, when used in combination, accelerate stone passage and also decrease the stone passage time. In the present study, combination had an expulsion time of 7.96 days, which was shorter than the duration found by Jayant K et al., and Rahman MJ et al., [8,34]. Corticosteroids are a valuable addition to medical expulsive drugs, although they do not suffice as monotherapy [35,36]. Only short-term therapy with corticosteroids should be prescribed to avoid adverse effects, and it should be avoided in patients with diabetes, gastric ulcers, or steroid intolerance.

The present study confirms that in the management of lower ureteral stones (5-10 mm), the combination of silodosin plus tadalafil and tamsulosin plus tadalafil is the most effective drug intervention for MET. Silodosin plus tadalafil and tamsulosin plus tadalafil are also highly effective in pain control. There was no significant difference in side effects between all groups, and these were mild and well tolerated by the study patients, who were relatively younger and without any co-morbidities. The side effects were comparable to other studies [8,33,34,37], and no severe complications were recorded in any of the groups. In the case of silodosin (mainly) and tamsulosin, abnormal ejaculation was the main side effect observed [14,25]. Silodosin tends to cause fewer peripheral vasodilation-related complications than tamsulosin [14,38]. The ejaculatory problems are reversible after withdrawal from the drug, so they do not compromise the general health of the patients.

The present study confirms that the silodosin-tadalafil combination was more effective in terms of expulsion rate, expulsion time, and pain episodes compared to other combinations. Silodosin used at a dose of 8 mg daily for medical expulsion was well tolerated in this study. The synergistic action of the alpha blocker and PDE inhibitor not only increases stone expulsion but also decreases the need for surgical intervention (ureteroscopy) in lower ureteric calculi, thereby decreasing the need for hospital stay as well as economic burden on medical reimbursement schemes. The strength of the present study is that it compared the effects of various agents individually as well as in combination therapy.

Limitation(s)

The present study was a single-centre small-scale study with a short duration of treatment, and it did not assess the effect of these drugs in the mid ureter and proximal ureter. Therefore, large-scale multicentre studies need to be conducted to generalise these results at a wider level.

CONCLUSION(S)

The alpha blocker-tadalafil combination was more effective in terms of expulsion rate and expulsion time without a significant increase in side effects. Combination therapy of silodosin with tadalafil and tamsulosin with tadalafil may be effectively used in ureteric calculi in the 5-10 mm range. Newer molecules are being researched persistently for use in conservative management and medically-driven ureteric calculus expulsion therapy. Permutation combinations of available drugs with proven safety can help us achieve better results.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 21, 2023
- Manual Googling: Mar 17, 2023
- iThenticate Software: Jun 27, 2023 (14%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 19, 2022**
Date of Peer Review: **Feb 15, 2023**
Date of Acceptance: **Jun 30, 2023**
Date of Publishing: **Sep 01, 2023**