A comparison of tamsulosin and silodosin versus tadalafil in medical expulsive therapy for distal ureteral stone in men: a prospective study

Abstract

Objectives: To evaluate the efficacy of tamsulosin, silodosin, and tadalafil as medical expulsive therapy for distal ureteral stones in men.

Methods: Adult males meeting the inclusion criteria were randomized into one of four treatment arms - dexketoprofen (control group), tamsulosin (Group 1), silodosin (Group 2), and tadalafil (Group 3). The stone expulsion rate after four weeks represented the primary endpoint, while the stone expulsion rate at the end of the study and the incidence of adverse events constituted secondary endpoints. Clinical findings were compared between all four drug groups.

Results: No statistically significant difference was observed among the groups in terms of age, body mass index, stone futures, expulsion time, pain episodes, or total analgesic use. Expulsion rates in the fourth week were 42.5%, 80%, 82.5%, and 75%, respectively. The stone expulsion rates in groups 1, 2, and 3 were significantly higher than in the control group ($p < 0.001$). However, the differences between groups 1, 2, and 3 were not statistically significant. No serious adverse effects were observed during the study period.

Conclusion: The study results showed a higher expulsion rate in male patients using tamsulosin, silodosin and tadalafil for distal ureteral stones, but no significant superiority between these. All three are safe, effective, and well-tolerated, causing minimal side-effects.

Keywords: Distal ureteral stones, Male, Medical expulsive therapy**,** Dexketoprofen, Tadalafil, Tamsulosin, Silodosin

INTRODUCTION

As in the rest of the world, various precautionary measures were adopted in our country during the global coronavirus disease 2019 pandemic, and all non-emergency operations were cancelled. Clinicians have had to turn to non-invasive methods in the treatment of diseases due to the pandemic. One such disease is ureteral stone. Medical expulsive therapy (MET) is a non-invasive medical treatment used in ureteral stones aimed at achieving spontaneous stone expulsion through relaxation of the smooth ureteral muscles and reduction of peristaltic activity (1). Stone passage depends on two main factors, those involving the stone, and those involving the urinary system. Stone-related factors include the stone size, number, and location within the urinary system. Urinary system-related factors include ureteric spasm, mucosal edema or inflammation, and the ureteric anatomy (2). The objective in MET is to achieve spontaneous stone passage through relaxation of the smooth muscles of the ureter and by reducing peristaltic activity.

High densities of the three alpha-1 receptor subtypes (alpha 1a, 1b, and 1d) occur in the distal third of ureteric smooth muscle. Alpha blocker therapy suppresses basal smooth muscle tone, and peristaltic frequency and amplitude, while preserving tonic propulsive contractions, resulting in a decrease in intra-ureteric pressure and an increase in fluid transport (3). Use of alpha-1 adrenergic receptor blockers thus facilitates stone passage. Tamsulosin, which exhibits high uroselectivity as well as comparable alpha-1a and 1d activity, and silodosin, a more selective alpha-1a adrenergic receptor antagonist, are widely employed in research and are of proven efficacy in MET (4).

Phosphodiesterase-5 inhibitors (PDE-5is) act on the smooth muscle nitric oxide/cyclic guanosine monophosphate signaling pathway and produce ureteral relaxation. The lumen of the ureter is thus dilated, allowing stones to pass spontaneously. One direct meta-analysis

showed that the PDE-5i tadalafil can effectively treat distal ureteral calculi as MET (5). Although tadalafil has been employed to treat sexual dysfunction and lower urinary tract symptoms, its use in MET for ureteral stones is extremely limited. The number of studies comparing the efficacy of silodosin and tadalafil is very small. Tamsulosin is the alpha-1 adrenoreceptor antagonist most frequently evaluated for the purpose of MET, and is of proven effectiveness (6). Dexketoprofen tramadol (DT) is a non-steroidal anti-inflammatory agent frequently used in our county, as was given to the control group in the present study. This study aimed to analyze the safety and efficacy of three different drugs in distal ureteral stones and also to compare the efficacy of tamsulosin, silodosin, versus tadalafil.

PATIENTS AND METHODS

Male patients were enrolled in this study from March 2020 to January 2021. All patients were informed about MET and the study aims once approval had been obtained from the xxx xxx University ethical committee. Written consent was obtained from all patients agreeing to participate in the study.

Patient Selection and Evaluation

Patients receiving MET due to distal ureteral stone and meeting the inclusion criteria were enrolled in this prospective study. Stone length was evaluated from non-contrast computed tomography (CT) by the reporting radiologist. The localization of distal ureter was defined as distal to the region where the ureter crosses over the iliac artery.

Inclusion criteria

- Male patients aged 18 – 55

- Patients with a single stone 4 – 9.9 mm in size in the distal ureter

Exclusion criteria

- Patients with two or more unilateral stones or bilateral stones

- Patients aged 56 or more (since the anatomy of the intertrigonal region will change in association with potential benign prostatic hyperplasia)

- Female patients (since the anatomy of the intertrigonal regions differs to that in men)

- Individuals with fever or urinary tract infections

- Individuals with kidney failure or severe hydronephrosis

- Patients with a solitary kidney

- Patients with horseshoe kidney, a duplex urinary system, or a history of ureter strictures

- Current use of alpha adrenoceptor antagonists or daily tadalafil

- Patients with known drug allergies

One hundred seventy-six patients met the inclusion criteria during the study period. However, four were excluded due to unwillingness to participate, and 12 due to being lost to follow-up (Figure 1).

Procedures

The patients were divided into four groups, a control group receiving dexketoprofen 50 mg, Group 1 receiving tamsulosin 0.4 mg, Group 2 receiving silodosin 8 mg, and Group 3 receiving tadalafil 5 mg daily. All participants were requested to drink two liters of water every day and to use a sieve for stone collection after urine filtration. Patients were also permitted to use 1 g intramuscular (IM) metamizole for analgesia on demand. Patients were advised to present to hospital in case of intractable acute pain, fever, urinary tract infection, or nausea and vomiting. Patients' clinical conditions were monitored by means of weekly telephone interviews. These were conducted by a research fellow and investigated whether or not the stone had passed, the patient's clinical state, and development of any drug-related side-effects. MET was discontinued in case of severe pain despite IM metamizole, adverse events, severe hydronephrosis, kidney failure, fever, or urinary tract infection, if the patient expressed a desire for stone removal, and ureteroscopic lithotripsy (UL) was performed. Patients who reported expelling their stones underwent CT to confirm their stone-free status (Figure 2). Clinically stable patients who were unable to expel their stones or who were uncertain whether or not they had done so were invited to attend controls on the 14^{th} and 28^{th} days. Stone and hydronephrosis status were assessed using CT. Patients also underwent routine urine culture, complete urine, and kidney function tests. UL was recommended to

patients who were unable to expel their stones at the end of 28-day follow-up. Patients who refused surgery and were in a stable clinical condition continued to receive active follow-up. The study was concluded with the application of UL to the last patients unable to achieve spontaneous stone passage at the end of 56 days.

Stone expulsion rates, stone expulsion times, rates of UL, numbers of colic episodes, analgesic doses, and side-effects associated with MET were evaluated and compared separately between the groups at the end of the study.

Statistical analysis

SPSS 25 (Statistical Package for Social Sciences- IBM Corp., Armonk, NY, USA) software was employed for data analysis. A p values < 0.05 were considered statistically significant. Normality of measurable data was assessed using the Kolmogorov-Smirnov test. The Kruskal-Wallis test was applied to assess statistically significant differences among the groups. The chi-square test was employed to test the association between expulsion rates and side-effects. The Bonferroni post-hoc test was applied to determine the differences between pairwise groups in order to identify the source of significance in variables found to be significant.

RESULTS

No statistically significant differences were observed between the groups in terms of patient body mass index, age, stone side, stone size, expulsion time, pain episodes, or average dosage of metamizole. The patient characteristics and results are shown in Table 1.

Two-week stone expulsion rates were 40% (16 out of 40 patients) in the control group, 62.5% (25 out of 40) in Group 1, 65% (26 out of 40) in Group 2, and 62.5% (25 out of 40) in Group 3. The differences between the groups were evaluated using the chi-square test and were found to be statistically insignificant ($p = 0.05$).

Four-week stone expulsion rates were 42.5% (17 out of 40 patients) in the control group, 80% (32 out of 40) in Group 1, 82.5% (33 out of 40) in Group 2, and 75% (30 out of 40) in Group 3. Statistically significant differences were determined between the groups ($p < 0.001$). The stone expulsion rate after four weeks differed significantly between the control group and Group 1, the control group and Group 2, and the control group and Group 3. Groups 1, 2 and 3 exhibited a statistical advantage over the control group in terms of stone expulsion after four weeks. However, no statistically significant superiority in terms of efficacy was observed between groups 1, 2 and 3. Post-hoc analyses for expulsion proportions in the study and the results obtained are given in Table 2.

Three patients in the control group declining UL at the end of the fourth week, three in Group 1, one in Group 2, and two in Group 3, continued with medical treatment. No patients expelled stones during follow-up in the control group, Group 1 or Group 2, but stone passage occurred in one patient in Group 3. The rates of stone passage at the end of the study in the control group and groups 1, 2, and 3 were 42.5%, 80%, 82.5% and 77.5%, respectively. The differences were statistically significant between the control group and groups 1, 2, and 3 ($p <$

0.001). However, no significant difference was observed between groups 1, 2, and 3 (Table 2).

No severe drug-associated adverse effects were recorded in the groups. Headache and backache were more frequent in Group 3, and gastritis was significantly more common in the control group ($p < 0.05$). Retrograde ejaculation was observed only in groups 1 and 2, with no significant difference between these two groups ($p = 0.055$). Greater orthostatic hypotension was reported in the control group and groups 1 and 2, and was more frequent in Group 1, but this was not statistically significant ($p = 0.1$). Adverse effects are shown in Table 3.

DISCUSSION

American Urological Association (AUA) and European Association of Urology (EAU) clinical guidelines support the use of MET for distal ureteral calculi. However, neither guideline sets out the ideal stone size for MET, nor the ideal length of treatment (6 – 8). One study reported wide variation in observed spontaneous passage rates, between 71% and 98% for distal ureteral stones less than 5 mm in size and between 25% and 53% for stones 5 – 10 mm in size, with a mean expulsion time exceeding 10 days (9). The AUA states that spontaneous passage rates increase the smaller the stone and that MET may be suitable for distal stones with a size of 10 mm (6). However, the EAU emphasizes the possibility of differences among patients, and that it is not possible to estimate an exact cut-off size for stones with a high likelihood of being passed spontaneously, although it cites a best approximation of less than 10 mm. Small stones (less than 6 mm) have also been described as ideal for MET (8).

There is no specific information available for the duration of MET, although many authors have reported a follow-up time of four weeks (5, 10). The AUA recommends that observation of patients with complete unilateral ureteral obstruction should not exceed six weeks in order to avoid irreversible kidney damage (6). As with the typical size of stone, the EAU also gives no specific follow-up time, merely reporting that informed patients not developing any complications (such as infection, refractory pain, or deterioration of renal function) may be placed under observation (8).

Numerous medical therapies have been investigated in the context of MET, including antispasmodics, corticosteroids, alpha blockers, calcium channel blockers, PDE-5is, and combinations thereof (11). Alpha blockers are currently the only monotherapy recommended for use as MET by the EAU (8). Significantly higher success rates have been reported in

patients using alpha blockers in the treatment of distal ureteral stones less than 10 mm in size compared to patients receiving placebo or no treatment (77.3 vs 54.4%, respectively) (6). A meta-analysis of alpha blockers compared to controls determined a statistically significant absolute increase of 29% in stone-passage rates (7). PDE-5is have recently frequently been employed for MET, and one meta-analysis described tadalafil (OR: 1.84; 95% CI, 1.60 – 2.12) and sildenafil (OR: 2.26; 95% CI, 1.41 - 3.62) as markedly superior to placebo (11). The success rate for tadalafil in distal ureteral stones smaller than 10 mm ranges between 66.7% and 84.1% (12 - 15).

Analysis of stone expulsion rates after four weeks, the first endpoint of this study in the control group and groups 1, 3, and 3 revealed 42.5%, 80%, 82.5% and 75% efficacy, respectively. The success rates of tamsulosin, silodosin and tadalafil were significantly higher compared to the control group. All three drugs exhibited comparable efficacy among themselves.

Randomized controlled studies comparing tamsulosin and silodosin in distal ureteral stones smaller than 10 mm have reported significantly high success rates of 57 - 64.4% and 80.3 - 84%, respectively. However, the success rate for tamsulosin in those studies is relatively lower than that in other studies (15 – 17). In contrast to those studies, Ye et al.'s randomized controlled study of 3296 patients (1642 in the tamsulosin group and 1654 in the placebo group) yielded as success rate for tamsulosin of 86% (10). In their meta-analysis, Tao et al. reported a success rate for tamsulosin in distal ureteral stones of 67 - 90.7% (18). In terms of tamsulosin success rates, the present study is consistent with Ye et al. and Tao et al.

Some studies involving male and female patients have determined significantly higher success rates for silodosin compared to tamsulosin (15 - 17), but not others (19, 20). Success rates for tamsulosin and silodosin in the present study were 80% and 82.5%, respectively, and the

difference between them was not statistically significant. The equivalent rates were 82% and 88% in Imperatore et al., and 72.4% and 78.6% in Arda et al. similarly to the present research, both these studies found no significant difference between tamsulosin and silodosin (19, 20). However, men and women were enrolled in both those studies, while our study involved only young/middle-aged men. This represents the major difference between those studies and our own research.

The stone expulsion rate for tadalafil in the fourth week exceeded 75%. Randomized controlled studies in the literature have reported success rates for tadalafil between 66.7% to 84.1% (12 – 15). Success rates for tadalafil were significantly higher than those for tamsulosin in two of those studies (13, 14), but not in two others (12, 15). The only randomized controlled study in the literature comparing tadalafil monotherapy and silodosin therapy reported success rates of 83.3% for silodosin and 66.7% for tadalafil, the difference being significant ($p = 0.016$) (15). The effect of tadalafil was found to be similar to those of silodosin and tamsulosin in the present study.

Stone expulsion rates at the end of the study, the second endpoint were 42.5% in the control group, and 80%, 82.5% and 77.5% in groups 1, 2, and 3, respectively. Observation was maintained in case of patients with no clinical impairment and unwilling to undergo UL at the end of four weeks in this study. However, stone passage occurred in one patient from the tadalafil group during this time. UL was applied to the other patients, and our study indicates that an observation period exceeding 28 days provided no additional benefit to patients.

Stone expulsion rates after two weeks in the control group and groups 1, 2, and 3 indicated 40%, 62.5%, 65% and 62.5% efficacy, respectively ($p = 0.05$). Similarly to the present study, Dell'Atti reported success rates for tamsulosin and silodosin at the end of two weeks of 43.2% and 69.69%, while Arda et al. reported rates of 58.3% and 62.3%, respectively (17, 20).

One previous study reported that antispasmotics, watchful waiting, and placebo yielded low rates of stone passage, while higher rates were achieved with alpha blockers and PDI-5s (11). The control group in the present study was given dexketoprofen, which is frequently used in our county, with a success rate of 42.5%. Similarly to the present study, Arda et al. reported 50% success for watchful waiting. The AUA has reported a success rate of 54.4% for placebo or no treatment. The stone expulsion rate in the control group in the present study was lower than in these two studies (6, 20). However, both men and women were enrolled in both those studies, while our study involved only young/middle-aged men. We attribute the low rate in the present study to the enrollment of a specific patient group.

No significant differences were determined between the groups in this study in terms of expulsion time, pain episodes, or total analgesic use. In contrast to our study, a randomized, controlled study involving male and female patients and comparing tamsulosin, silodosin and tadalafil monotherapies found that silodosin was superior to tamsulosin and tadalafil in terms of expulsion time, pain episodes, and total analgesic use (15). Similarly to the present research, another previous study comparing tadalafil and tamsulosin also reported no difference in expulsion time, pain episodes, or total analgesic use (14).

In addition to the endpoints of our study, when the drugs were compared in terms of common side-effects, significant differences were observed in terms of headache, backache and gastritis, but no difference was determined in orthostatic hypotension or retrograde ejaculation. Consistent with previous studies, retrograde ejaculation, a more specific alpha blocker side-effect, was more common in patients using silodosin (15 – 17, 19). The prevalences of backache (15%) and headache (15%) in the tadalafil group in the present study were significantly higher than in the control group. However, there was no significant difference between groups, 1, 2, and 3 in terms of backache or headache. Consistent with the present research, other studies comparing tadalafil and tamsulosin have also observed no

significant intergroup differences in terms of backache or headache (12 - 15). From that perspective, this study is compatible with the previous literature.

CONCLUSION

MET appears to be a more effective method for the medical treatment of distal ureteral stones between 4 mm and 9.9 mm in size in adult males. Our results indicated no statistically significant superiority in terms of efficacy or duration between tamsulosin, silodosin and tadalafil for distal ureteral stones with minimal drug side effect.

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Table 1. Patient characteristics and the results of the study

Variables	Control group (n = 40)	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	p
Age (years), mean ± SD (range)	39.77 ± 10.2 (19 - 55)	40.77 ± 11.5 (18 - 55)	41.32 ± 10 (21 - 55)	39.57 ± 9.8 (21 - 55)	0.86
Body mass index (kg/m²), mean ± SD	26.46 ± 2.7	27.25 ± 3.3	27.51 ± 3.4	27.58 ± 4	0.39
Side, N (%)					0.96
Right	21 (52.5%)	19 (47.5%)	21 (52.5%)	20 (50%)	
Left	19 (47.5%)	21 (52.5%)	19 (47.5%)	20 (50%)	
Stone size (mm), mean ± SD, (range)	6.01 ± 1.81 (4 – 9.2)	5.94 ± 1.56 (4 – 9.9)	6.04 ± 1.26 (4 - 9.1)	6.29 ± 1.74 (4 – 9.9)	0.67
Expulsion rate (%), (after two weeks)	40% (16/40)	62.5% (25/40)	65% (26/40)	62.5% (25/40)	0.05
Expulsion rate (%), (after four weeks)	42.5% (17/40)	80% (32/40)	82.5% (33/40)	75% (30/40)	< 0.001
Expulsion rate (%), (end of study)	42.5% (17/40)	80% (32/40)	82.5% (33/40)	77.5% (31/40)	< 0.001
Expulsion time (day), mean ± SD (range)	13.1 ± 10.02 (3 – 56)	13.1 ± 9.3 (3 – 47)	10.77 ± 6.3 (2 – 35)	11.92 ± 6.5 (2 – 33)	0.76
Pain episodes, mean ± SD	0.67 ± 0.85	0.72 ± 0.71	0.65 ± 0.83	0.55 ± 0.71	0.68
Average dosage of metamizol (g)	0.8 ± 1.06	0.82 ± 0.9	0.77 ± 0.97	0.65 ± 0.83	0.81

Table 2. Post-hoc analyses for expulsion rates

	Week 4	End of the study
	p	**p**
Control group vs. Group 1	0.001	0.001
Control group vs. Group 2	0.001	0.001
Control group vs. Group 3	0.006	0.003
Group 1 vs. Group 2	1	1
Group 1 vs. Group 3	0.789	1
Group 2 vs. Group 3	0.585	0.78

Variable, N (%)	Control group (n = 40)	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	p
Retrograde ejaculation	0	2 (5%)	4 (10%)	0	0.055
Headache	0	3 (7.5%)	5 (12.5%)	6 (15%)	0.009
Orthostatic hypotension	1 (2.5%)	4 (10%)	1 (2.5%)	0	0.1
Backache	0	2 (5%)	2 (5%)	6 (15%)	0.04
Gastritis	10 (25%)	2 (5%)	1 (2.5%)	3 (7.5%)	0.001

Table 3. Adverse events in each group

LEGENDS

Figure 1. Patient enrollment algorithm (DT: Dexketoprofen trometamol; T: Tamsulosin; S: Silodosin; Td: Tadalafil)

Figure 2. Computed tomography images of patients (a: before treatment; b: after treatment; arrow: stone)