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ORIGINAL PAPER

Tadalafil versus alpha blockers (alfuzosin, doxazosin, tamsulosin and silodosin) as medical expulsive therapy for < 10 mm distal and proximal ureteral stones

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Summary ***Objectives: To evaluate the effect of tadalafil compared with four alpha blockers (alfuzosin, doxazosin, tamsulosin and silodosin) as medical expulsive treatment for ureteral stones in male adults.***
Materials and methods: Male adults who were admitted to urology clinic with flank pain and diagnosed with non complicated < 10 mm ureteral stone on non-contrast computed tomography (NCCT) between June 2014-September 2015 were retrospectively evaluated. A total of 273 patients with ureteral stone were divided into five groups. Alfuzosin 10 mg/daily, doxazosin 8 mg/daily, tamsulosin 0.4 mg/daily, silodosin 8 mg/daily and tadalafil 5 mg/daily for 6 weeks were prescribed respectively. Stone localization, diameter, volume and Hounsfield units were noted as NCCT findings. The patients were divided into the two groups based on their stone localization as distal and mid-proximal stones. These two groups were evaluated separately. Expulsion rate were noted at the end of 6 weeks. NCCT and treatment findings were compared between five drug groups in distal and mid-proximal stones separately.
Results: Age was higher in tadalafil group in distal stones (p = 0.032). Expulsion rate was found 78.1% for alfuzosin, 75.7% for doxazosin, 76.5% for tamsulosin, 88.6% for silodosin and 90% for tadalafil in distal (p = 0.44) and 21.7%, 30%, 30%, 30% and 54.5% in mid-proximal stones (p = 0.034) respectively.
Conclusions: Expulsion rate was higher in silodosin and tadalafil for distal ureteral stones but the difference didn't meet statistical significance. However the expulsion rate was significantly higher in tadalafil than in the other groups for mid-proximal ureteral stones. The result of this study showed that tadalafil may increases ureteric stone expulsion.

KEY WORDS: *Alpha blockers; Medical expulsive theraphy; tadalafil; Ureteral stone.*

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INTRODUCTION

Urinary tract stone disease is most prevalent between the ages of 20 and 40 years and 3 times more common in men than women (1). Twenty percent of all urinary tract stones are found in the ureter and many of these stones should be treated with efficacious treatment modalities such as extracorporeal *shock wave lithotripsy* (SWL) and endoscopic laser or pneumatic lithotripsy with *ureterorenoscopy* (URS) (2, 3). But these treatments include some risks such as complications of treatment, failure and high cost. Therefore, some predictors were determined on *non-contrast computed tomography* (NCCT) of stone diameter, stone volume, *Hounsfield units* (HU) and *Hounsfield density* (HD) to reduce these risks (4). For ureteral stones, although the watchful waiting approach has been reported to be associated with spontaneous stone expulsion for about 50% of ureteral stones, some complications may occur such as urinary tract infections, hydronephrosis and colic events (3). *Medical expulsive therapy* (MET), another method for stone expulsion, has become routine in the treatment of obstructive ureteral calculi in recent years. The use of various drugs as MET, which affect the ureter via different mechanisms, can reduce symptoms and facilitate stone expulsion. Alpha and beta adrenergic receptors were found in the ureter (5). Alpha-1 and particularly subtype alpha-1D are the most commonly observed adrenergic receptor subtypes in the ureteral smooth muscle cells (6). Alpha blockade has been proven to decrease peristaltic activity, contraction and intraureteral pressure and to improve spontaneous stone passage and decrease both the time to stone passage and analgesic requirements (7, 8). According to *European Association of Urology Guidelines*, alpha-blockers are recommended for MET because they should ensure well controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve (9). A phosphodiesterase-5 (PDE-5) inhibitor (*tadalafil*), which acts on the NO/cGMP signaling pathway of smooth muscles, causes ureteral relaxation (10). A recent study reported that *tadalafil* showed a high ureteral stone expulsion rate and significant pain control (11).
Alpha blockers and *tadalafil* in MET have a proven role to promote stone passage and reduce the need for minimally invasive surgery for distal ureteral stones. However, these findings were not investigated for proximal ureteral stones. In related studies only two of three drugs were compared for MET with distal ureteral stones. Therefore we wanted to evaluate the possible effect of *tadalafil* compared with alpha blockers, which are alfuzosin, doxazosin, tamsulosin and silodosin, for MET in uncomplicated distal and proximal ureteral stones in male adults.

No conflict of interest declared.

Material and methods

After approval obtained from the Local Ethics Committee, we retrospectively reviewed the records of > 18 year old male patients with uncomplicated ureteral stones of < 10 mm diameter on NCCT images between June 2014 and September 2015. After the informed consent, only male patients were included in the study to standardize patients and to eliminate the differences in expulsion time depending on anatomical differences between female and male patients. There is also an indication problem for tamsulosin, silodosin and *tadalafil* treatment for female patients in our country. Therefore only male patients were selected for the study. Patients who had not previously received any alpha blocker or *tadalafil* treatment were treated with alpha blockers or PDE-5 inhibitor for 6 weeks. Patients who had only ureteral stone and were treated with one of four alpha-blockers (alfuzosin 10 mg/daily (*Xatral, Sanofi Aventis*), doxazosin 8 mg/daily (*Cardura, Pfizer*), tamsulosin 0.4 mg/daily (*Tamprost, Zentiva*), silodosin 8 mg/daily (*Urorec, Recordati*)) as MET were included in the study. Patients who had concomitant erectile dysfunction and did not accept the use of alpha blockers were treated with *tadalafil* 5 mg/daily (*Cialis, Lilly and Lifta, Abdi Ibrahim*) for possible effect of ureteral stones expulsion and erectile dysfunction treatment. Patients who were diagnosed with nephrolithiasis, > 10 mm ureteral stones, bilateral ureteral stones, ureteral stones requiring drainage or obstructive, grade 3 hydronephrosis, multiple ureteral stones and any anatomical abnormalities on NCCT examination were excluded from the study. Patients with urinary tract infection, fever and elevated creatinine level were also excluded.

All patients who had unsuccessful MET underwent *shock wave lithotripsy* (SWL) or *ureterorenoscopic* (URS) treatment. Demographic data of included patients (age, height, weight and *body mass index* (BMI)) were noted. Before MET, NCCT images using 2 mm sections with the liver's dome as cranial border and pubis joint as caudal border at 100 mA 120 kV (*Alexion TSX-034A, Toshiba®, Japan*) were taken. The localization of stone, the stone diameter, the stone volume, grade of hydronephrosis, the distance of stone from ureterovesical junction (for distal stones) as described by *Yuceturk CN et al.* (12), the distance of stone from ureteropelvic junction (for proximal stones), *Hounsfield units* (HU) and *Hounsfield density* (HD) of the stone measured by NCCT were noted. All measurements were calculated by one radiologist. Largest stone diameters were measured on longitudinal, transverse, and axial images and mean stone diameter was calculated as the average of these three values. HU and stone volume were calculated with computed tomography viewer program. HD was calculated as the HU divided by mean stone diameter (13). All patients were divided into five drug groups as alfuzosin, doxazosin, tamsulosin, silodosin and *tadalafil* groups. Drug groups were subdivided into two groups according to the stone localization on NCCT images as distal and mid-proximal ureteral stones and were evaluated separately. For stone localization, the anatomical limit of ureteral parts was defined as the level of the iliac artery crossing the ureter. Below this area was defined as distal, while above this area was defined as mid-proximal. Time interval follow-up of MET was 6 weeks. Patients were instructed to take diclofenac 50 mg tablets orally during episodes of pain, and filter their urine to detect stone expulsion. Expulsion time was noted when the stone was observed in the filtered urine. Suspicious expulsions or unsuccessful expulsion of stone were confirmed with NCCT at the end of the 6th week. Treatment findings (expulsion success rate and expulsion time) were noted at the end of MET. Demographic data of patients, NCCT findings and treatment findings were compared between drug groups for distal and mid-proximal ureteral stones separately. The primary endpoint expected from the study is the expulsion rate for alpha-blockers and *tadalafil* groups. The secondary endpoint is expulsion times for the groups. Finally an important endpoint is the *tadalafil* expulsion success for mid-proximal ureteral stones.

Statistical analysis

Demographic data of patients were analyzed and compared for all groups. The parameters measured on NCCT (the stone diameter, grade of hydronephrosis, the stone volume, the distance of stone from ureterovesical junction, the distance of stone from ureteropelvic junction, HU and HD) were compared between all 5 groups.

The Pearson $\chi 2$ test and Kruskal-Wallis test were applied between the groups for nonparametric statistical analysis using commercially available software (*Statistical Package for the Social Sciences, Version 20.0; SPSS, Chicago, III*).

The alpha level of statistical significance was set at .05.

Results

Male adults who were admitted to the urology clinic with flank pain and diagnosed with uncomplicated ureteral

Table 1.
Demographic data, tomography findings and expulsion findings of the study population.

Variables	All patients (n = 273)
Age, year; mean ± SD (range)	41 ± 11.3 (20.3-80)
Height, cm; mean ± SD (range)	1.74 ± 6 (161-190)
Weight, kg; mean ± SD (range)	82.7 ± 13.7 (56-125)
BMI, kg/m^2; mean ± SD (range)	27.2 ± 4.1 (18.3-39.9)
Percentage of stone localization	
Distal	61.5
Mid-Proximal	38.5
Mean stone diameter, mm; mean ± SD (range)	4.9 ± 1.7 (1-10)
Stone volume, mm^3; mean ± SD (range)	80.3 ± 83.5 (0.5-502)
The distance of distal ureteral stone from ureterovesical junction, mm; mean ± SD (range)	9.7 ± 4.3 (1-22)
The distance of mid-proximal ureteral stone from ureteropelvic junction, mm; mean ± SD (range)	84.9 ± 37.7 (29-152)
HU; mean ± SD (range)	571.2 ± 307.8 (89-1384)
HD, HU/mm; mean ± SD (range)	114.5 ± 40 (41.4-280.5)
Percentage of hydronephrosis grade	
None	16.9
Grade 1	53.1
Grade 2	30
Grade 3	0
Percentage of expulsion success rate	63
Expulsion time, day; mean ± SD (range)	11.3 ± 9.5 (2-39)

Abbreviations: BMI, Body Mass Index; HU, Hounsfield Units; HD, Hounsfield Density.

stone on NCCT between June 2014 and September 2015 were retrospectively evaluated.

A total of 273 male adults were included in the study. Mean age was 41 ± 11.3 (20.3-80) years and mean BMI was 27.2 ± 4.1 (18.3-39.9) kg/m^2 for the whole group. Mean age, height, weight, BMI, stone localization, mean stone diameter, stone volume, the distance of stone from ureterovesical junction, the distance of stone from ureteropelvic junction, HU, HD, grade of hydronephrosis, stone expulsion rate and expulsion time are given in Table 1 for all patients.

Considering the stone localization there were 168 patients with distal and 105 patients with mid-proximal ureteral stones. In drug groups; 55 patients were treated with alfuzosin, 57 with doxazosin, 54 with tamsulosin, 55 with silodosin and 52 with *tadalafil*. In the drug groups 32, 37, 34, 35 and 30 patients had distal, and 23, 20, 20, 20 and 22 patients had mid-proximal ureteral stones, respectively. There was no significant difference in the demographic data (height, weight and BMI) of the five groups for distal and mid-proximal ureteral stones ($p > .05$) (Table 2 and 3).

Age was higher in the *tadalafil* group than the other groups for distal ureteral stones ($p = .032$) (Table 2).

Table 2.

Comparison of computed tomography findings and expulsion rate and time between alfuzosin, doxazosin, tamsulosin, silodosin and tadalafil groups of MET in distal ureteral stones.

Distal ureteral stones (n = 168) Variables [a]	Alfuzosin (n = 32)	Doxazosin (n = 37)	Tamsulosin (n = 34)	Silodosin (n = 35)	tadalafil (n = 30)	P value
Age, year; median ± SD	41.7 ± 13.3	38.2 ± 12.8	43.9 ± 11.5	39.2 ± 11	46.3 ± 9.9	.026
Height, cm; median ± SD	172.9 ± 5.7	175.1 ± 4.8	175.2 ± 7.4	176.3 ± 5.2	178 ± 1.7	.322
Weight, kg; median ± SD	82 ± 14	82.6 ± 11	82.1 ± 12.6	82.3 ± 10.9	85.7 ± 12.2	.663
BMI, kg/m^2; median ± SD	27.4 ± 3.9	26.9 ± 3.4	26.6 ± 2.8	27.2 ± 3.7	27.1 ± 4.3	.542
Stone diameter, mm; median ± SD	4.9 ± 1.4	4 ± 1.7	4.5 ± 1.8	4.5 ± 1.7	4.7 ± 1.8	.227
Stone volume, mm^3; median ± SD	75.1 ± 73.1	48.6 ± 56.5	68.9 ± 94.4	66.3 ± 69.7	75.1 ± 84.5	.220
The distance of stone from ureterovesical junction, mm; median ± SD	9.5 ± 4.2	9.6 ± 4.9	9.1 ± 3.8	9.5 ±3. 6	10.9 ± 5.1	.66
Hounsfield units, HU; median ± SD	527.2 ± 270.6	442.5 ± 269.3	461.3 ± 291.6	491.8 ± 287.5	494.2 ± 268.4	.471
Hounsfield density, HU/mm; median ± SD	103.5 ± 35.9	111.1 ± 36.1	99.8 ± 34.2	104.8 ± 34.7	105.2 ± 35.9	.689
Percentage of hydronephrosis grade 2	18.7	21.6	129.4	37.1	33.3	.404
Percentage of expulsion rate	78.1	75.7	76.5	88.6	90	.44
Expulsion time, day; median ± SD	11.7 ± 5.7	11.6 ± 7.2	9.5 ± 7.6	10.9 ± 10.1	5.7 ± 3.4	.019

BMI, Body Mass Index; HU, Hounsfield Units.
[a] Continuous variables were compared by Kruskal-Wallis test.

Table 3.

Comparison of computed tomography findings and expulsion rate and time between alfuzosin, doxazosin, tamsulosin, silodosin and tadalafil groups of MET in mid-proximal ureteral stones.

Mid-proximal ureteral stones (n = 105) Variables [a]	Alfuzosin (n = 23)	Doxazosin (n = 20)	Tamsulosin (n = 20)	Silodosin (n = 20)	Tadalafil (n = 22)	P value
Age, year; median ± SD	40.8 ± 10.7	39.6 ± 8.7	39.1 ± 10.4	37.8 ± 13.1	41.2 ± 8.3	.765
Height, cm; median ± SD	172 ± 4.9	175.3 ± 4.6	172.5 ± 6.6	173.2 ± 5.6	172.7 ± 5.7	.525
Weight, kg; median ± SD	89.6 ± 16.4	91.7 ± 19.7	77.7 ± 13	83.6 ± 15.7	79.2 ± 8.3	.177
BMI, kg/m^2; median ± SD	30.3 ± 5.7	29.8 ± 5.8	26.2 ± 4.4	27.8 ± 4.9	26.6 ± 2.3	.147
Stone Diameter, mm; median ± SD	5.3 ± 1.8	5.2 ± 1.2	5.3 ± 1.6	6 ± 1.2	5.7 ± 1.6	.251
Stone Volume, mm^3; median ± SD	101.8 ± 102.2	79.4 ± 52.7	100.4 ± 115.3	123.5 ± 61.2	119 ± 100.9	.207
The distance of stone from ureteropelvic junction, mm; median ± SD	84.4 ± 37.1	77.6 ±35.2	90.7 ± 36.3	81.2 ± 40.6	90.8 ± 40.8	.889
Hounsfield units, HU; median ± SD	672.6 ± 294.2	606.7 ± 241.9	775 ± 259.6	721.7 ± 344	838.7 ± 327.2	.125
Hounsfield density, HU/mm; median ± SD	127.5 ± 48.7	116.4 ± 36.9	145.7 ± 38.3	116.6 ± 42.2	143.9 ± 35	.062
Percentage of hydronephrosis grade 2	26.1	30	30	40	40.1	.185
Percentage of expulsion rate	21.7	30	30	30	54.5	.034
Expulsion time, day; median ± SD	26 ± 5.6	18 ± 20.8	10.7 ± 12.4	8.3 ± 6	18.3 ± 14.7	.191

BMI, Body Mass Index; HU, Hounsfield Units.
[a] Continuous variables were compared by Kruskal-Wallis test.

NCCT findings of the drug groups are given in Table 2 and 3. There was no significant difference in stone diameter, stone volume, the distance of stone from ureterovesical junction, the distance of stone from ureteropelvic junction, HU, HD and grade of hydronephrosis between the five groups with distal and mid-proximal ureteral stones ($p > .05$). Expulsion rate was 78.1% for alfuzosin, 75.7% for doxazosin, 76.5% for tamsulosin 88.6% for silodosin and 90% for *tadalafil* for distal ureteral stones and 21.7%, 30%, 30%, 30% and 54.5% for mid-proximal ureteral stones, respectively.

Median expulsion time was 11.7 days for alfuzosin, 11.6 days for doxazosin, 9.5 days for tamsulosin, 10.9 days for silodosin and 5.7 days for *tadalafil* for distal and 26, 18, 10.7, 8.3 and 18.3 days for mid-proximal ureteral stones, respectively. Expulsion rates for silodosin and *tadalafil* groups with distal ureteral stones were higher than the other three groups, but this result was not statistically significant ($p = .44$).

Expulsion time for the *tadalafil* group was significantly lower than the other drug groups with distal ureteral stones ($p = .019$) (Table 2). Expulsion rate of the *tadalafil* group was significantly higher than the other groups with mid-proximal ureteral stones ($p = .034$). However, there was no statistically significant difference between the groups in terms of expulsion time for mid-proximal ureteral stones (Table 3).

Discussion

In brief, the expulsion rate was higher in silodosin and *tadalafil* groups compared to the other groups for distal ureteral stones, but did not reach statistical significance between the groups (expulsion rate was 78.1%, 75.7%, 76.5%, 88.6%, and 90% for alfuzosin, doxazosin, tamsulosin, silodosin and *tadalafil*, respectively). However, the expulsion rate was significantly higher in the *tadalafil* group compared to the other groups for mid-proximal ureteral stones (21.7%, 30%, 30%, 30% and 54.5%, respectively). Also, age was higher in the *tadalafil* group than in the other groups for distal ureteral stones.

In *European Association of Urology* (EAU) guidelines, MET, SWL and URS are recommended in the treatment of ureteral stones (9). In recent studies, some possible and accurate predictors were determined that affect the success of SWL and URS (4, 14). These predictors were stone diameter, stone volume, HU, and HD of ureteral stones and grade of hydronephrosis on NCCT. Therefore, in our study these factors were equivalent in the drug groups to reduce the effect on MET.

According to previous studies, the expulsion rate of distal ureteral stones during watchful waiting is 25-54% with mean expulsion time > 10 days. To increase the expulsion rate and decrease the analgesic requirements, medical therapy is recommended for distal ureteral stones (15-18). In an AUA/EAU panel, two medical therapies, which are calcium channel blocker and alpha-receptor antagonists, were optionally recommended for distal ureteral stones.

The meta-analysis of six studies of alpha blockers (280 patients) yielded an expulsion rate of 81% (19).

There are several studies that show no significant difference between expulsion rates of alpha-blockers for distal ureteral stones. Alfuzosin expulsion rates were reported as 85.6% in a randomized controlled prospective study (20). In a recent randomized, placebo-controlled trial comparing placebo, tamsulosin and nifedipine as MET for distal, middle and proximal ureteral stones, there was no significant difference between the groups (21).

In a recent meta-analysis, there was no statistically significant difference in stone expulsion rate and time between alfuzosin and tamsulosin (22). In a study evaluating alfuzosin and doxazosin as MET for distal ureteral stones, expulsion rates and time were reported as 52.9% and 7.38 ± 5.55 days with alfuzosin, 62% and 7.85 ± 5.11 days with doxazosin, respectively (23).

In a prospective randomized study comparing silodosin with tamsulosin, the efficacy of silodosin (high selective antagonist of alpha-1A receptor) was shown to be superior to tamsulosin (alpha-1D and alpha-1A receptors selective antagonist) (24, 25). *Tadalafil*, which is a smooth muscle relaxant, has recently been approved by the US *Food and Drug Administration* (FDA) for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia and erectile dysfunction (10). *Gratzke et al.* demonstrated the role of the PDE-5 inhibitors of vardanafil, sildenafil and *tadalafil* in relaxation of ureteral muscles (26-29).

In a recent study *Kumar et al.* detected significantly higher expulsion rate and lower expulsion time in a silodosin group compared to tamsulosin and *tadalafil* groups for distal ureteral stones (11).

In another recent study which compared the expulsion rate and expulsion time of tamsulosin with the combination of *tadalafil* and tamsulosin, higher expulsion rate and lower expulsion time were detected in the tamsulosin plus *tadalafil* group (83.6% and 14.9 ± 4.4 days) compared with the tamsulosin group (65.5% and 16.7 ± 4.8 days) (30).

In this study, we divided ureteral stones into two groups according to their localization as distal and mid-proximal. For distal ureteral stones, the stone expulsion rates with silodosin and *tadalafil* were higher than alfuzosin, doxazosin and tamsulosin, but the difference did not reach statistical significance. However, expulsion time in the *tadalafil* group was lower than in alpha blocker groups (alfuzosin, doxazosin, tamsulosin and silodosin) for distal ureteral stones. We found a higher expulsion rate in the *tadalafil* group compared to alpha-blockers (alfuzosin, doxazosin, tamsulosin and silodosin) for mid-proximal ureteral stones and that was statistically significant. However, expulsion time was not found to be statistically significant between the groups. Alpha-blockers and PDE-5 inhibitors have separate mechanisms that increase the stone expulsion compared to watchful waiting. Successful combination of tamsulosin and *tadalafil* used by *Jayant et al.* opened up the potential use of a combination of silodosin with *tadalafil* (11, 30).

The limitations of this study are that it is retrospective, non-randomized and has a limited number of patients in drug groups for ureteral stones. Due to the retrospective nature of the study, three major parameters, which were

quantity of additional analgesic usage, frequency of acute renal colic and emergency visits of patients, could not be evaluated. Also, age was higher and expulsion time was lower in the *tadalafil* group than in the other groups for distal ureteral stones. The explanation of this result may be that stone expulsion was a rapid condition of the *tadalafil* usage or that elderly patients could expel stones more easily due to possibly more compliant ureters. Another limitation is that concomitant erectile dysfunction was only present in the *tadalafil* group. However, additional drug usage or concomitant diseases were not significantly different between the groups.
Finally the important result of the study and the difference from the other studies is that 5 mg daily *tadalafil* usage is associated with high stone expulsion success in patients diagnosed with mid-proximal ureteral stones.

Conclusions

The result of this study indicates that *tadalafil* showed a significantly lower stone expulsion time compared with alpha-blockers for distal ureteral stones.
The most important finding is the higher expulsion rate with *tadalafil* for mid-proximal ureteral stones compared with alpha-blockers.
Therefore this situation opens up the potential use of a combination of *tadalafil* and silodosin for distal and mid-proximal ureteral stones and this combination of *tadalafil* in MET may reduce the need for SWL therapy and minimally invasive procedures. However, there is a need for large prospective randomized studies to clarify these findings.

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