

## Efficacy of Silodosin Dose in Medical Expulsive Therapy for Distal Ureteral Stones: A Retrospective Study

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**Purpose:** We aimed to investigate the efficacy of silodosin 4 mg/day and 8 mg/day for medical expulsive therapy (MET) of lower ureteral stones.

**Materials and Methods:** We retrospectively analyzed the medical records of 161 patients admitted to urology clinics of Ahi Evran University Medical Faculty and Ankara Training and Research Hospital with distal ureteral stones and treated with MET with different doses of silodosin between January 2013 and August 2015. 81 patients were treated with silodosin 4mg/day in group-1 and 80 patients with silodosin 8mg/day in group-2. Age, gender, complaints on admission, stone size, the distance between the stone and ureterovesical junction, stone passage rate, duration of stone passage after starting MET, and adverse effects were noted from the charts of the patients, and the groups were compared.

**Results:** There were 81 patients in group-1, and 80 patients in group-2. Two groups were similar for age ( $P = .38$ ) and gender ( $P = .92$ ). Spontaneous stone passage was seen in 41 (50.9%) patients in group-1, and in 59 (73.8%) patients in group 2. The groups were different for spontaneous stone passage rate ( $P = .002$ ). In group-1, 10 (25%) patients that could not pass their stones spontaneously and were treated with extracorporeal shockwave lithotripsy (SWL), and 30 (75%) of them were treated with ureterolithotripsy. Eight (38%) patients that could not undergo ureterolithotripsy and/or anesthesia and were not able to pass their stones were treated with SWL, and 13 (62%) patients were treated with ureterolithotripsy in group-2. All of the patients were stone free at the end of the treatment.

**Conclusion:** A dose of 8 mg/day should be preferred if silodosin is to be preferred for MET in lower ureteral stones.

**Key Words:** adrenergic  $\alpha$ -blockers; lower ureteral stones; medical expulsion therapy; nephrolithiasis; silodosin; urolithiasis

### INTRODUCTION

Urolithiasis is one of the most frequent diseases of the urinary tract. It has a multifactorial etiology and affects approximately 12% of the population. Currently, minimally invasive techniques are used for surgical treatment of urinary stones in every level of the urinary system. Technological advances provided progress in the surgical treatment of urinary stones, however, the same developments could not be achieved when medical treatment options are considered.<sup>(1,2)</sup>

Demonstration of alpha- adrenergic receptors in distal one-thirds of the ureter, and evidence regarding the effects of those receptors on smooth muscle contraction showed that they played an important role in the ureter physiology.<sup>(3)</sup> Understanding those physiologic factors enabled the use of alpha receptor blockers for medical treatment of distal ureteral stones. EAU guidelines recommended use of alpha receptor blockers for medical expulsive therapy (MET) of distal ureteral stones.<sup>(4)</sup> Alpha blockers such as tamsulosin and doxazosin have

been used in several studies for MET in distal ureteral stones.<sup>(5)</sup> Silodosin is a new molecule used for the treatment of benign prostate hyperplasia, and it has been used for MET.<sup>(6,7)</sup> There is no consensus on the dose or duration of treatment for those agents. In our study, we compared the effectiveness of 4 mg/day and 8 mg/day silodosin used for MET.

### MATERIALS AND METHODS

#### Study Population

After obtaining ethical permission in local ethical committee of Ankara Training and Research Hospital we retrospectively analyzed the medical records of 161 patients admitted to urology clinics of Ahi Evran University Medicine Faculty and Ankara Training and Research Hospital with distal ureteral stones and treated with medical expulsive therapy (MET) with different doses of silodosin between January 2013 and August 2015.

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Received August 2016 & Accepted December 2016

**Table 1.** Patient and stone characteristics

Variables	Group-1 (n= 81)	Group-2 (n= 80)	P Value
Age,years Mean $\pm$ SD (range)	37.9 $\pm$ 14.6 ( 17-71)	36.1 $\pm$ 13.2 (17-72)	.38
Gender, no(%)			
Male	39	41	.92
Female	42	39	
Stone size ,mm Mean $\pm$ SD (range)	5.0 $\pm$ 2.1 (2-10)	5.1 $\pm$ 1.8 (2-9)	.90
Stone size			
< 5 mm	45	48	.56
(< or > 5 mm)	36	32	

### Procedure

From the patients' records ,we extracted 161 patients who had undergone MET, 81 patients were treated with silodosin 4mg/day in group-1 and 80 patients with silodosin 8mg/day in group-2. All patients had received silodosin therapy for four weeks.

### Evaluation

In our study, lower ureter was considered as the part of the ureter between the ureterovesical (UV) junction and the place where ureter crossed iliac vessels. The patients that had a solitary stone in this part of the ureter, and treated with 4 mg/day or 8 mg/day oral silodosin for MET were included in the study. The exclusion criteria were the presence of a stone or another disorder in other parts of the ureter, bilateral lower ureteral stones, need for an early surgical intervention, high fever, and septic findings. The patients that stopped MET by their own wills (may be due to the side effects like hypotension and retrograde ejaculation) and who preferred other treatment methods were not also included in the study. In two medical center, all medical records were selected randomly. We were not able to find detailed information in some medical records. So we did not take them into consideration and they were not included in our study. The records that we selected were the best kept ones.

Urinalysis, blood urea and creatinine levels, and complete blood counts of all patients were obtained on admission, and during treatment. Kidney-ureter and bladder (KUB) X-ray and spiral computerized tomography (CT) without contrast were used as imaging modalities on admission. The patients that had MET were called for weekly follow-ups, and KUB X-ray and/or urinary ultrasonography (USG) was used to determine the degree of hydronephrosis. Urinalysis was used to determine hematuria and urinary infection. The stone size

was considered as the longest diameter of the stone. The size of the stone, the distance of the stone to the UV junction, presence of hydronephrosis, and any other additional disorders were analyzed on CT.

Age, gender, complaints on admission, stone size, the distance between the stone and UV junction, duration of stone passage after starting MET, stone passage rate, and adverse effects were noted from the charts of the patients, and the groups were compared. The additional therapies used in patients with unsuccessful MET were evaluated.

The patients in group-1 were administered 4 mg/day silodosin, and the ones in group-2 were administered 8 mg/day silodosin. All patients were recommended oral hydration. Analgesics were given to be used when needed. Antibiotics were added to the treatment in case of urinary infection.

Any patients who were not stone free after 4 weeks of follow-up with MET were treated with SWL or ureteroscopy. Success was considered as the passage of stone during MET, and the duration of treatment was noted.

### Statistical analysis

SPSS 21.0 package program was used for data analysis. Normality of distribution was analyzed with Kolmogorov-Smirnov and Shapiro-Wilk tests. Skewness and Kurtosis values were also measured. "Independent samples *t*-test" was used for pairwise comparisons with a normal distribution, and "Mann-Whitney *U*" test without normal distribution. "Pearson's Chi-Square" test was used to compare the categorical variables.  $P < .05$  was considered as statistically significant.

### RESULTS

Patients and stone characteristics in groups were summarized in **Table 1**. The groups did not show significant differences for age ( $P = .38$ ) or gender ( $P = .92$ ).

**Table 2.** Outcomes of medical expulsive therapy with different doses of silodosin in groups

	Group-1	Group-2	P
Successful n(%)	41 (50.9 %)	59 (73.8 %)	.002
Unsuccessful n(%)	40 (59.1 %)	21 (26.2 %)	
The time of spontaneous stone passage , day Mean $\pm$ SD (range)	16.49 $\pm$ 6.67 (6 – 28)	16.02 $\pm$ 6.73 (5 – 28)	.73
The number of analgesic usage Mean $\pm$ SD (range)	2.26 $\pm$ 1.11 (0-5)	2.01 $\pm$ 1.00 (0-4)	.14

**(Table 1)**

Patient and stone characteristics and outcomes of medical expulsive therapy with different doses of silodosin in groups were summarized in **Tables 1 and 2**, respectively.

The duration for stone passage ranged between 6 and 28 days ( $16.49 \pm 6.67$  days) in group-1 while this duration was between 5 and 28 days ( $16.02 \pm 6.73$  days) in group-2. There was no statistically significant difference between the groups for the duration of stone passage ( $P = .73$ ). (**Table 2**)

The need for analgesics during treatment was between 0 and 5 times ( $2.26 \pm 1.11$  times) in group-1, and between 0 and 4 times ( $2.01 \pm 1.00$  times) in group-2. The groups were similar for the need for analgesics ( $P = .14$ ).

The mean stone size was  $4.05 \pm 1.80$  mm in the ones that passed their stones spontaneously, and  $6.10 \pm 1.95$  mm in the ones that could not pass their stones spontaneously in group-1, (95% CI: -2.97 to -1.32, OR= -2.14,  $P < .001$ ). Those values were  $4.61 \pm 1.52$  mm and  $6.43 \pm 1.63$  mm, respectively, in group-2, (95%CI: -2.62 to -1.04, OR= -1.83),  $P < .001$ ). There was a statistically very significant association between stone size and ability to pass the stone spontaneously in both groups.

The distance between the stone and UV junction was between 0 and 34 mm ( $16.73 \pm 7.49$  mm) in patients that passed their stones spontaneously, and between 8 and 32 mm ( $19.18 \pm 7.39$  mm) in patients that could not pass their stones spontaneously in group-1 ( $P = .33$ ). Those distances were between 0 and 32 mm ( $17.49 \pm 8.25$  mm), and between 8 and 32 mm ( $19.33 \pm 6.65$  mm), respectively in group-2 ( $P = .16$ ). There was no significant association between the distance of the stone to UV junction and spontaneous passage of the stone in neither groups.

Retrograde ejaculation occurred in 4 (5%) and 7 (9%) patients in groups-1 and 2, respectively. Hypotension did not occur in any of the patients in group-1, however, hypotension was seen in 3 (4%) patients in group-2. In group-1, 10 (25%) patients that could not pass their stones were treated with SWL, and 30 (75%) patients were treated with ureterolithotripsy. Six patients that were first treated with SWL had ureterolithotripsy later. The stones were cleared in all patients. Eight (38%) patients that could not pass their stones were treated with SWL, and 13 (62%) patients were treated with ureterolithotripsy in group-2. Five patients that were first treated with SWL had ureterolithotripsy later. All of the patients were stone free at the end of the treatment. In our study groups, we did not encounter any complications higher than grade II according to the Clavien classification.

## DISCUSSION

In our study, we retrospectively analysed patients with distal ureteral stones who were treated by different doses of silodosin in two medical centers. Our aim was to find out an answer to the efficacy of silodosin dose in MET.

In our study, the groups did not show significant differences for age ( $P = .38$ ), gender ( $P = .92$ ) or stone size ( $P = .90$ ). The main result of our study was in the stone expulsion rate. A significant statistical difference was noted between the two groups (50.9% vs 73.8%) ( $P =$

.002) The other significant statistical difference was obtained from the stone size in both groups. In each group, spontaneous stone passage was higher in stones with  $< 5$  mm.(group 1,  $P < .001$ )(group 2,  $P < .001$ ). Although in stones with  $< 5$  mm, watchful waiting is a therapeutic option,  $\alpha 1$  blockers in MET reduce analgesic usage by decreasing the frequency of contractions in the ureter that means reducing the episodes of ureteral colic.<sup>(8)</sup> In our study, two different silodosin doses were efficacious for reducing pain and decreasing the amount of analgesic administered. The groups were similar for the need for analgesics ( $P = .14$ ).

In addition, expulsion time was similar in both groups and showed no statistically significant difference ( $P = .73$ ). Edema and the shape of the stones are the main factors influencing expulsion time and stone expulsion rate even in stones with  $< 5$  mm in diameter.<sup>(9)</sup> To overcome this problem, an alternative but an effective therapeutic approach; ureteroscopy can be safely performed.<sup>(10)</sup> In our study, in some of the patients with no stone passage after MET, we treated them by ureteroscopy. In the ureteroscopic interventions, we saw that there was a severe inflammatory reaction of stone impacted mucosa with edematous changes. Therefore, patients who were not stone free after 4-week follow-up by medical therapy, stones were most likely impacted and needed a different alternative approach.

Different treatment options such as ureterolithotomy, ureterolithotripsy, and SWL have been employed in the treatment of lower ureteral stones. A wait-and-see approach may be used as an option in patients that do not prefer surgery as the first treatment option. In the literature, spontaneous passage of lower ureteral stones was reported as 68%, and this rate was reported as 25-53% in the stones sized between 5 and 10 mm.<sup>(11,12)</sup> The possibility of spontaneous passage is lower in ureteral stones bigger than 10 mm since they are impacted to the ureter, therefore surgery should be preferred as the first treatment option in those cases.<sup>(13)</sup>

Adding  $\alpha$ -adrenergic receptor blockers to treatment increases stone passage rate in patients who are followed up for spontaneous stone passage. Placebo-controlled studies have been performed to investigate use of  $\alpha$ -blockers for MET in the case of ureteral stones.<sup>(6)</sup> Although the presence of  $\alpha$ -1 adrenergic receptors have been shown in the proximal and medial parts of the ureter, distal ureter has the highest concentration for  $\alpha$ -1 adrenergic receptors.<sup>(14)</sup> The  $\alpha$ -1d,  $\alpha$ -1a and  $\alpha$ -1b subtypes of  $\alpha$ -1 adrenergic receptors are found in the distal ureter, in rank order.<sup>(15)</sup> This is why MET is most efficient in the case of distal ureteral stones. In literature, 0.4 mg tamsulosin and 8 mg silodosin have been used for MET in case of distal ureteral stones. The studies that compared tamsulosin with a control group reported the success rate as 79-90% in tamsulosin group, and as 53-58% in the control group.<sup>(16-19)</sup> The studies that compared silodosin and tamsulosin reported better success rates with silodosin in distal ureteral stones.<sup>(20-21)</sup> Silodosin 8 mg/day was compared with the control group, and a significantly higher success rate was reported with silodosin.<sup>(22)</sup> In the same study, it was reported that use of tamsulosin for the expulsion of stones sized  $\geq 5$  mm resulted in a better success rate when compared to the control group (75.9% vs. 17.9%). However, the expulsion rate was higher in the control group when compared to tamsulosin group in

case of the stones sized < 5 mm (92.9% vs. 69.2%). A multicenter, randomised, placebo-controlled trial by Pickard et al. demonstrated that tamsulosin and nifedipine were not effective at decreasing the need for further treatment to achieve stone clearance in 4 weeks for patients and found no difference in spontaneous passage during 4 weeks treatment between groups.<sup>(23)</sup> However many prospective randomized studies should be done not only with these drugs but with the other  $\alpha$ -blockers in order to support this comment. In our study, we compared 4 mg/day and 8 mg/day silodosin for MET. We determined a significantly higher success rate in 8 mg/day silodosin group. The success rate with 4 mg/day silodosin was found as 50.9% in our study. The success rates of the control groups in the studies that compared  $\alpha$ -blockers for MET with the control groups are similar to the success rate we obtained with 4 mg/day silodosin in our study.<sup>(17,18,21)</sup> In these studies, patients' included criteria and demographics of those control groups may be different than the patients in our silodosin 4 mg group that's why stone expulsion rate may be similar. In the literature, it was reported that the stone passage rate was shorter in patients that were given silodosin for MET when compared to the control group in case of lower ureteral stones ( $9.29 \pm 5.91$  days vs.  $13.40 \pm 5.90$  days).<sup>(21)</sup> In our study, the duration for stone passage in case of spontaneous stone passage was between 6 and 29 days (mean:  $16.49 \pm 6.67$  days) in group 1, and between 5 and 28 days (mean:  $16.02 \pm 6.73$  days) in group 2.

Alpha 1d adrenoreceptors are predominate, particularly in the distal ureter. Silodosin is 56-fold and 583-fold more selective for  $\alpha$ -1a when compared to  $\alpha$ -1d and  $\alpha$ -1b, respectively. The hypotensive effect of alpha receptor blockers decreases as their selectivity increases. However, an increase is seen in the frequency of retrograde ejaculation. A meta-analysis that reported silodosin as more effective than placebo and tamsulosin in the case of distal ureteral stones found only an insignificant increase in abnormal ejaculation.<sup>(22)</sup> In our study, we found higher rates of hypotension and retrograde ejaculation in the group that used a higher dose of silodosin, although those findings did not reach statistical significance. The adverse effect rate expectedly increases as the dose of alpha-receptor blockers increases. In group 1 hypotension did not occur in any of the patients and retrograde ejaculation in 4 patients lower than group 2. From that point of view, silodosin 4 mg may be preferred when patients do not withstand these side effects. In our study, most likely urologists used lower dose of silodosin for MET in distal ureteral stones for this reason. However, 8 mg silodosin was much more effective in stone expulsion and although there were side effects, all patients in this group completed the study.

The patients should be closely followed up during MET for the adverse effects that could develop due to obstruction in the case of distal ureteral stones. In case of severe pain, urinary infection, pyonephrosis, and rupture of the fornix, MET should be stopped, and surgery should be planned. In our study group, there were no complications necessitating cessation of MET. The patients were treated with other interventions when they could not pass their stones spontaneously.

There are some limitations in our study. At first, its design is retrospective. The absence of a control group

may seem to be a problem but our aim is to evaluate the efficacy of silodosin in the MET for distal ureteral stones and want to examine whether the lower dose of silodosin is effective or not. The data obtained from two urology departments pointed out that lower dose of silodosin had been used by many urologists for distal ureteral stones. Starting from this point of view, we designed our study and to our knowledge, it may be probably the first study on different doses of silodosin on distal ureteral stones. We believe that our results could help in guiding the urologists to review their preferences on the dose of silodosin for distal ureteral stones  $\leq 10$  mm. The stone expulsion percentage between men and women may be the other limitation. However, the objective of the present study was to observe stone expulsion rate.

## CONCLUSIONS

In our study, we concluded that for treatment of lower ureteral stones sized 2-10 mm, MET with silodosin 8 mg is quite an effective method in patients when watchful waiting approach is appropriate. This option may be used safely in patients that may tolerate pain and do not prefer surgery as the first treatment option. Due to the low incidence of side effects, low dose of silodosin may be used but when considering expulsion rates, silodosin 8 mg can be the reason for preference among urologists.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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