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Original article

Efficacy of Silodosin versus Silodosin plus Tadalafil as Medical Expulsive Therapy for Lower Ureteric Stones: A Prospective Randomized Placebo Controlled Study

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Abstract

Purpose: To compare the efficacy of silodosin, silodosin plus tadalafil and placebo as a medical expulsive therapy (MET) for distal ureteral calculi. **Subjects & methods***:* This prospective randomized clinical trial was conducted on 120 renal colic patients with distal ureteric stones (5-10mm) over a period of 6 months (1st February 2022 to 1st August 2022). The patients were randomly divided into three equal groups. Patients included in group **A** received Placebo treatment once daily, in group **B** received Silodosin 8 mg once daily, while patients in group **C** received Silodosin 8 mg in combination with tadalafil 10mg once daily. Therapy was given for a maximum of 4 weeks. Stone free rate, time to stone expulsion, dose and duration of nonsteroidal anti-inflammatory drugs (NSAIDs), hospital visits due to pain, and adverse effects induced by the drugs were recorded. **Results:** The expulsion rate significantly differed between the studied groups ($P < 0.001$). Post hoc analysis revealed it was significantly higher in group C (87.5%) and B (72.5%) than in group A (47.5%), with no significant difference between groups B and C ($P < 0.05$). Regarding expulsion time, there was a significant difference between the studied groups ($P < 0.001$), and post hoc analysis revealed it was significantly lower in group C (10 ±3 days) than in groups B (14 ±5) and A (21 ±4). Additionally, it was significantly lower in group C than in group B. **Conclusion**: Medical expulsive therapy for distal ureteric stone using Tadalafil in combination with silodosin is safe, well tolerated, and more effective than silodosin alone.

Key words: ureteral stones; tadalafil; silodosin.

Introduction:

Urolithiasis is a common urological condition, with a lifetime prevalence of approximately 10%, and a recurrence rate of up to 50% within five years. Shock wave lithotripsy (SWL) has become a standard therapy for upper urinary tract calculi with a success rate of 50-95%. However, SWL has been associated with several side effects, including pain, hematuria, and obstructive uropathy, and it may require multiple sessions to achieve a satisfactory result (1).

Recently, several alpha-1 adrenergic receptor antagonists (α1-blockers) such as Tamsulosin, Silodosin, and Alfuzosin have been used as an adjunct to SWL to facilitate the expulsion of the stone and improve patient outcomes. α1-blockers act on the smooth muscle cells of the ureter, reducing ureteral tone and increasing ureteral diameter, which may promote the passage of the stone (2).

Despite the growing popularity of α1-blockers for the treatment of urolithiasis, the optimal dosage and duration of treatment remain unclear. In addition, there is a lack of consensus regarding the efficacy of α1-blockers in the expulsion of stones, and the incidence of side effects associated with their use varies widely among studies (3).

Therefore, the present study aims to investigate the efficacy and safety of α1-blockers as an adjunct to SWL in the treatment of urolithiasis. We hypothesize that α1-blockers will improve the expulsion rate and decrease the time to expulsion, compared to placebo or no treatment. Moreover, we aim to identify the optimal dosage and duration of treatment that would maximize the benefit-to-risk ratio for patients. The findings of this study may provide valuable insights into the management of urolithiasis and contribute to the development of evidence-based guidelines for the use of α1-blockers in this context.

Patients and Methods: This randomized placebo-controlled study was conducted at the urology department in Benha university hospital over a period of 6 months (1st February 2022 to 1st August 2022). Patients aged 18-60 years and with lower ureteric stone from 5mm to 10mm in size, diagnosed by non-contrast CT scan, Ultrasonography or X-ray KUB, and given informed written consent were only included in the study. After approval of the study by the ethical committee of Faculty of Medicine, Benha University and from 179 patients assessed only 120 were enrolled to this study. Patients were randomized and divided into three equal

groups based on a computer-generated random number. **Group A:** patients received Placebo treatment once daily, **Group B:** Patients received Silodosin 8 mg once daily and Group **C:** Patients received Silodosin 8mg in combination with Tadalafil 5 mg once daily.

Patients with multiple ureteric stones, radiolucent stones, urinary tract infection, pregnancy, pediatric population and history of ureteral surgery or previous endoscopic procedures and patients who did not give written consent were excluded from this study. Moreover, the exclusion criteria also extended further to include patients having ischemic heart disease, congestive cardiac failure, or complicated hypertension, raised serum creatinine and those requiring emergency intervention (**Figure 1)**.

Patients were instructed to drink plenty of water and filter their urine to detect any passing stones. In case of pain patients were instructed to take diclofenac 75mg PO or 100mg injection according to severity of pain episode. Follow up was done weekly until stone passage or 4 weeks of treatment were completed before progress to ureteroscopy for stone extraction. Other incidents like intractable pain, rising creatinine or progressive hydronephrosis were also considered**.**

Primary outcome: The primary outcome was the stone expulsion rate.

Secondary outcomes: expulsion time, number of pain episodes, hospital visits, amount of analgesics, and side effects induced by the drugs.

The follow-up plan was as follows: All patients were advised to attend the outpatient clinic after 7 days of the first visit for clinical and radiological evaluation. In addition, patients were advised to return to the clinic immediately in case of any severe pain or any other complication. Stone expulsion was assessed by abdominal X-ray or ultrasound at 4 weeks after the initial visit. If the stone was still present after 4 weeks, a non-contrast computed tomography (NCCT) was performed to confirm its presence, and the patient was excluded from the study. The patients were followed up for 4 weeks after the initiation of the treatment to record any side effects of the drugs, analgesics consumption, number of pain episodes, and number of hospital visits. The follow-up period was considered appropriate since it is known that most stones pass within 4 weeks of the onset of symptoms, and the patients were followed up until the end of the study period.

Sample size:

The sample size calculation was done by G*Power 3.1.9.2 (Universitat Kiel, Germany). According to a previous study, the mean (± SD) score of stone expulsion rate immediately after the intervention was 47.5% ± 20.2% in group A, 72.5% ± 19.3% in group B, and 87.5% ± 8.7% in group C. The sample size was based on the following considerations: 0.44 effect size, 95% confidence limit, 80% power of the study, group ratio 1:1:1 and five cases were added in each group to overcome the dropout. Therefore, we recruited 120 cases (40 in group A, 40 in group B, and 40 in group C).

Statistical analysis:

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to normality, quantitative data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Quantitative data were compared between the studied groups using one-way ANOVA or Kruskal Wallis test for normally and non-normally distributed quantitative data, respectively. Categorical data were compared using the Chi-square test. Post hoc analyses were done in case of significant overall effect and were adjusted using Bonferroni's method. Multivariate logistic regression analysis was done to predict expulsion. Odds ratios with 95% confidence intervals were calculated. All statistical tests were two-sided. P values less than 0.05 were considered significant.

Research ethics committee: Ms.2.1.2022

Results:

There was no statistically significant difference between the groups regarding age (P = 0.16), sex (P = 0.778), and BMI (P = 0.226), also No significant differences were observed between the studied groups regarding stone size (P = 0.928) and side (P = 0.789). (***Table 1***).

The expulsion rate significantly differed between the studied groups (P < 0.001). Post hoc analysis revealed it was significantly higher in group C (87.5%) and B (72.5%) than in group A (47.5%), with no significant difference between groups B and C (P < 0.05). Regarding expulsion time, there was a significant difference between the studied groups (P < 0.001), and post hoc analysis revealed it was significantly lower in group C (10 ±3 days) than in groups B (14 ±5) and A (21 ±4). Additionally, it was significantly lower in group C than in group B (***Table 2***)

The number of *pain episodes* showed an overall significant difference between the studied groups (P < 0.001). Post hoc analysis revealed it was significantly higher in group A (median = 2) than in groups B and C (median = 1), with significant difference between groups B and C, also number of *hospital visits* showed an overall significant difference between the studied groups (P = 0.002), it was significantly lower in group C (median = 0, range = 0-2) than in groups A (median = 1, range = 0-3) and B (median = 0, range = 0-3), with no significant differences between groups B and C, in order to. *Amount of analgesics* showed an overall significant difference between the studied groups (P < 0.001). It was significantly lower in group C (median = 450 mg) than in groups B (median = 675 mg) and A (median = 750 mg), with no significant difference between groups A and B ***(Table 2)***.

Side effects significantly differed between the studied groups (P < 0.001). Post hoc analysis revealed it was significantly higher in group C (85%) than in groups A and B (22.5% and 52.5%, respectively). Also, it was significantly higher in group B than in group A. The most frequent side effects were dizziness in group A (44.4%), retrograde ejaculation in group B (33.3 %), and retrograde ejaculation with Backache and increased erection in group C (20.6%). (***Table 3***).

Multivariate logistic regression analysis was done to predict stone expulsion. The predictors were Silodosin use (associated with better expulsion, OR = 3.748, 95% CI = 1.187 – 11.837, P = 0.024), combined drug use (associated with better expulsion, OR = 14.002, 95% CI = 3.391 – 57.813, P < 0.001), and stone size (the bigger stone size, the less expulsion, OR = 0.292, 95% CI = 0.171 – 0.498, P < 0.001) (***Table 4***).

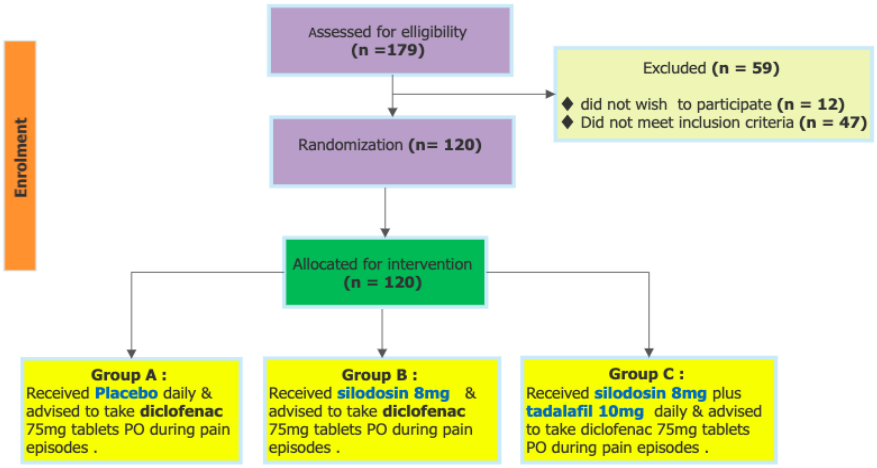

Figure 1: CONSORT flowchart of the studied patients.

Table 1: General characteristics of the studied groups

	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	P-value
Age (years)	36 ±7	39 ±8	37 ±8	0.16
Sex				
Males	27 (67.5)	24 (60)	25 (62.5)	0.778
Females	13 (32.5)	16 (40)	15 (37.5)	
Stone size	6.8 ±1.2	6.7 ±1	6.7 ±1.1	0.928
Stone side				
Right	23 (57.5)	21 (52.5)	24 (60)	0.789
Left	17 (42.5)	19 (47.5)	16 (40)	

Data were presented as mean ±SD or number (percentage)

Table 2: Clinical characteristics in the studied groups

	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	P-value
Expulsion rate	19 (47.5) [a]	29 (72.5) [b]	35 (87.5) [c]	<0.001* <0.05 (B vs C)
Expulsion time (days)	21 ±4 [a]	14 ±5 [b]	10 ±3 [c]	<0.001*
Number of pain episodes	2 (0 - 4) [a]	1 (0 - 3) [b]	1 (0 - 2) [c]	<0.001*
Number of Hospital visits	1 (0 - 3) [a]	0 (0 - 3) [b]	0 (0 - 2) [b]	0.002* 0.854 (B vs C)
Amount of analgesics (mg)	750 (300 - 1950) [a]	675 (450 - 1350) [a]	450 (75 - 1125) [b]	0.002*

a: group A, b: group B and c: group C, *: significant as P-value < 0.05.

Table 3: Side effects in the studied groups

	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	P-value
Side effects (no %)				
Backache	0 (0)	3 (14.3)	4 (11.8)	**NA**
Dizziness	4 (44.4)	3 (14.3)	4 (11.8)	
Headache	2 (22.2)	4 (19)	5 (14.7)	
Increased erection	0 (0)	0 (0)	7 (20.6)	
Myalgia	0 (0)	1 (4.8)	1 (2.9)	
Nausea	3 (33.3)	0 (0)	0 (0)	
Orthostatic hypotension	0 (0)	2 (9.5)	3 (8.8)	
Retrograde ejaculation	0 (0)	7 (33.3)	7 (20.6)	
Total	**9 (22.5) [a]**	**21 (52.5) [b]**	**34 (85) [c]**	**<0.001***

Table 4: Multivariate logistic regression analysis for prediction of expulsion

	OR (95% CI)	P-value
Age (years)	1.025 (0.956 - 1.099)	0.494
sex	1.549 (0.506 – 4.742)	0.443
BMI	0.955 (0.765 - 1.191)	0.683
Stone size	0.292 (0.171 - 0.498)	<.001*
Silodosin (Group B)	3.748 (1.187 – 11.837)	0.024*
Combination (Group C)	14.002 (3.391 – 57.813)	<.001*

* Significant; OR: Odds ratio; 95% CI: 95% confidence interval

Discussion:

Because the lower ureteric stones are considered one of the most symptomatic calculi, and significantly affect the patient's quality of life, they have drawn the attention of the researchers to find the ideal and effective medical therapy. Recently, several drugs have been used as MET for conservative treatment of lower ureteric stones due to their role in enhancing stone passage, shortening time to stone expulsion and reducing the pain episodes severity (4).

Silodosin, a predominant selective a-1A receptor blocker which has been approved for the treatment of LUTS/BPH, is an effective and safe drug for MET of distal ureteral stones and is clinically superior in terms of stone expulsion rate, stone expulsion time and analgesic requirements as compared to its

controls for stones with diameter of > 5 mm and < 10 mm (5).

Tadalafil, a phosphodiesterase 5 inhibitor by acting on smooth muscle nitric oxide/cyclic guanosine monophosphate signaling pathway can induce ureteral relaxation leading to dilation of its lumen. Although the combination of silodosin and tadalafil has greater potency than either drug alone for the treatment of LUTS associated with BPH, only few meta-analyses tested their combination in treatment of lower ureteric stones (6).

In our study Group C (Silodosin plus Tadalafil) patients exhibited better stone expulsion compared to group B (silodosin only) and group A (placebo), (87.5 % vs. 72.5 % vs. 47.5% respectively), with statistically significant difference between the three groups. Similarly another study came to the conclusion that Tadalafil and Silodosin when taken together significantly increase the rate at which lower ureteric stones are expelled, and that this rate is statistically higher than that of either drug alone (tamsulosin or Silodosin) (7). Stone free rate for combination therapy was 90% (36/40), compared to 77.5% (31/40) and 57.5% (23/40) for silodosin and tamsulosin, respectively. That also was in agreement with another study who reported that there was a statistically significant difference in the stone expulsion rate between silodosin plus tadalafil (88,46%) and silodosin alone (75%), (p value: 0,002). On the contrary another study reported that although the stone expulsion rate in the tamsulosin group was higher than that in the Tadalafil group (63.6 %) and the placebo group (56.8%), it was not deemed statistically significant (P=0.294) (8).

The higher stone free rate seen in the combination group may be attributed to the different mechanisms of the two drugs involved.

In the present study the mean expulsion time was shorter in group C (10 ±3 days) than in group B (14 ±5 days) and group A (21 ±4 days), with statically significant difference between the three groups (P < 0.001). Similarly another study found that the mean expulsion time was 11.48 (3.1) days when silodosin was used in combination with tadalafil instead of 14.33 (3.1) days when silodosin was used alone (p < 0.001) (9). And also according to another study there was significantly higher expulsion time in Tamsulosin group (P < 0.001) and Silodosin group (P < 0.001) compared to silodosin and tadalafil group, with expulsion time 15 vs 21 vs 12 respectively (7).

Regarding the number of pain episodes in our present study showed an overall significant difference between the studied groups, there

was an overall statistically significant difference between the three studied groups ($p < 0.001$). We also found that the number of hospital visits due to pain was significantly less in group C (Silodosin plus Tadalafil) compared to other groups. the amount of analgesics required for pain also showed statistically significant difference between the three groups, with lower amount of diclofenac sodium in group C (median = 450 mg) than in groups B (median = 675 mg) and C (median = 450 mg), with no significant difference between groups A and B. Similarly, two studies found that the combination of silodosin and tadalafil resulted in significantly fewer pain episodes than silodosin and tadalafil alone ($P<0.001$) (7, 9)**.** Also, another study showed significantly fewer episodes of pain with tadalafil plus tamsulosin as compared to tamsulosin alone (10), similarly a recent study demonstrated that patients in the tamsulosin plus tadalafil group had fewer pain episodes (2.02) compared to the tamsulosin group (2.32) (P value = 0.001) and showed significantly fewer emergency room visits. Furthermore, the average requirement for an analgesic (diclofenac) was significantly lower in the combination group than in the tamsulosin group (11).

In our study, the reported side effects were mild and well tolerated in all three groups. Even though these side effects were statistically significant between the three groups, they did not lead to drop out from the study and were easily managed. Similarly, another study reported no serious adverse effects (12), and a recent study showed that no statistical difference was detected for adverse drug effects except for retrograde ejaculation, which was significantly higher in tamsulosin group ($P < 0.001$) (13).Other drug-related adverse effects such as headache, dizziness, orthostatic hypotension, backache, and runny nose were comparable between the two groups.

Conclusion

Our study concludes that, compared to treatment with Silodosin alone, the combination of Silodosin and tadalafil significantly increases the distal ureteral stone expulsion rate with evident reduction in the expulsion time and pain episodes. Further studies are required on large sample sizes.

Abbreviations and Acronyms

BMI: body mass index; MET: medical expulsive therapy; LUTS: lower urinary tract symptoms; BPH: benign prostatic hyperplasia; KUB: kidney, ureter and bladder PDE5Is: phosphodiesterase-5 inhibitors; NO: nitric oxide; cGMP: cyclic guanosine monophosphate.

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