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Comparative Study between Silodosin and Tamsulosin in Expectant Therapy of Distal Ureteral Stones

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Abstract
Objective: To compare the efficacy and safety of silodosin against tamsulosin as medical expulsion therapeutic agent in stone lower 1/3rd ureter. ***Patients and Methods:*** One hundred fifty patients divided equally into 2 groups I and II received silodosin 8 mg and tamsulosin 0.4 mg respectively. Patients aged 18 years or older having single unilateral stone 10 mm or less were included in the study. Patients with bilateral or multiple stones, marked hydronephrosis, previous open or endoscopic surgery and having urinary infection were excluded. Patients were followed weekly for 4 weeks by ultrasonography, plain radiography of the urinary tract and CT of the urinary tract when indicated. ***Results:*** Silodosin showed better results against tamsulosin as stone expulsion rate in silodosin and tamsulosin groups was 82.4 and 61.5% respectively with significant difference ($p = 0.007$). Also, the stone expulsion time was significantly lower in silodosin against tamsulosin groups as it was 9.4 ± 3.8 vs. 12.7 ± 5.1 days in group I and II respectively ($p = 0.001$). The adverse effects were comparable with non-significant more retrograde ejaculation in the silodosin group. ***Conclusion:*** Silodosin showed better efficacy in the stone expulsion rate and time with comparable safety of both drugs, with nonsignificant more retrograde ejaculation in silodosin.

Introduction

Urolithiasis is a common disorder that is faced daily by urologists all over the world, affecting 12% of the population worldwide [1]. Ureteral stones affect 20% of the urolithiasis cases [2, 3], of which70% are in the dis-

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tal third of the ureter [2]. Shock wave lithotripsy and ureteroscopy (URS) have a high success rate in the management of distal ureteric stones (DUS), but these therapies are expensive and not without risks, and the complications of URS are ranging from postoperative stricture to perforations up to ureteric avulsion [3]. Expectant approach has been used for the initial therapy of DUS and the spontaneous passage of ureteral stones was approximately 50% with respect to some complications as urinary tract infections, hydroureteronephrosis, and episodes of renal colic [4]. Itoh et al. [5] declared that 3 alpha 1 adrenergic receptor sub types are present in the human ureter (alpha1A, alpha1D, alpha1B). The blocking of these receptors will facilitate the passage of stones and decrease the episodes of the colicky attacks and so decrease the requirement for analgesics [6].

Latest researches reported that the alpha1A subtype plays the most significant part in the phenylephrine-mediated contraction of the human isolated ureteral smooth muscles [7]. The selective alpha1A and D adrenoceptor blocker, tamsulosin, demonstrated a high efficacy in enhancing spontaneous passage of ureteral stones 10 mm or less [8]. Silodosin is a highly selective alpha1A adrenoceptor blocker that has 162 times more affinity for alpha1A than B, so it has less undesired effects on the regulation of blood pressure and it was effective as medical expulsive therapy (MET) for DUS [9]. The objective of the present study was to evaluate the efficacy, adverse effects, and safety of silodosin 8 mg versus tamsulosin 0.4 mg in the expulsion time and rate of DUS.

Patients and Methods

This prospective randomized study was conducted between April 2015 and June 2016 on 150 patients (94 male and 56 female), with their age ranging from 18 to 56 years. Patients aged 18 years or more, harboring unilateral single stone 5–10 mm in largest diameter, located in the lower 1/3rd of the ureter (between the inferior border of the sacroiliac joint and ureterovesical junction) were included in the study. Patients with single kidney, urinary tract infection, bilateral or multiple stones, marked hydronephrosis, and history of previous endoscopic or open ureteral surgery were excluded from this study. The sample size was calculated using Epi. Inf. 7 program software (WHO, Geneva, Switzerland), and the selected level of confidence interval was 95% with an error of 5% and the study power was 90%, the stone clearance rate was considered clinical equivalence, and the ratio between the 2 groups was 1:1. The study protocol was declared to all enrolled patients and a written informed consent was taken; this study was approved by the local Ethical Committee of Benha faculty of medicine.

All participants were investigated using pelvi abdominal ultrasonography (US), plain radiography of kidney, ureter, and bladder (KUB). In radiolucent stones, non-contrast CT of the urinary tract was done. The patients were randomly divided by the closed envelope method into 2 groups: in group I, 75 patients received silodosin 8 mg and in group II, 75 patients received tamsulosin 0.4 mg; all patients were advised to drink at least 2 liters of water and to filter their urine for detection of stone passage and inform us once the stone passed as the investigations were repeated to assure stone expulsion. For renal colicky pain, diclofenac sodium (75 mg injection) was prescribed.

The follow-up visits were weekly for 4 weeks and we repeated the US and KUB biweekly and non-contrast CT when indicated at the end of the 4 weeks for assuring stone expulsion and the state of increased hydronephrosis, for the patients who did not pass the stone during the study period (4 weeks) URS was done and stone retrieval occurred.

Statistical Analysis

The collected data were tabulated and analyzed using SPSS version 16 software (SPSS Inc., Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test (χ^2) was used to analyze categorical variables. Quantitative data were tested for normality using the Shapiro-Wilks test assuming normality at $p > 0.05$. Continuous variables were expressed as mean ± SD if normally distributed or median and range if not. Student t test was used to analyze normally distributed variables among 2 independent groups, while nonparametric variables were analyzed using Mann-Whitney U test for 2 independent groups. The accepted level of significance was stated at 0.05 ($p \leq 0.05$ was considered significant).

Results

The age of the patients in group I ranged from 18 to 56 years and in group II ranged from 20 to 56 years. The total number of patients enrolled in this study was 150 patients but 3 and 4 patients in groups I and II, respectively, discontinued the medication early due to dizziness and postural hypotension. Also 4 and 6 patients in groups I and II, respectively, were lost in the follow-up period. Hence, the total number analyzed was 68 patients in group I and 65 patients in group II. There was no significant statistical difference between the 2 groups regarding the patient's age, sex, stone size, and laterality (Table 1).

There was significant statistical difference between the 2 groups regarding stone expulsion rate 82.4% (56 of 68) in group I and 61.5% (40 of 65) in group II, ($p = 0.007$; Table 2).

There was also statistical significant difference between the 2 groups regarding stone expulsion time as the stones passed rapidly and shortly in group I at a mean (SD) 9.4 ± 3.8 vs. 12.7 ± 5.1 days in group I and II respectively ($p = 0.001$; Table 2).

Table 1. Comparison between study groups regarding demographic and stone characteristics

	Group I (n = 68)	Group II (n = 65)	Test of significance	p value
Age, mean ± SD	34.5±9.8	34.8±9.7	St."t" = 0.17	0.87
Gender, n (%)				
Male	44 (64.7)	43 (66.2)	χ^2 = 0.031	0.86
Female	24 (35.3)	22 (33.8)		
Stone size, mm				
Mean ± SD	7.47±1.41	7.54±4.3	Z_{MWU} = 0.26	0.79
Median (range)	8 (5–10)	8 (5–10)		
<6	8 (11.8)	8 (12.3)	χ^2 = 0.009	0.92
6–10	60 (88.2)	57 (87.7)		
Laterality, n (%)				
Left	31 (45.6)	27 (41.5)	χ^2 = 0.22	0.64
Right	37 (54.4)	38 (58.5)		

Z_{MWU}, Z value of Mann-Whitney U test.

Table 2. Comparison between study groups regarding stone passage

	Group I (n = 68)	Group II (n = 65)	χ^2	p value
Stone passage, n (%)				
Not passed	12 (17.6)	25 (38.5)	7.17	0.007
Passed	56 (82.4)	40 (61.5)		
	Group I (n = 56)	Group II (n = 40)	Z_{MWU}	p value
Stone expulsion time in days				
Mean ± SD	9.4±3.8	12.7±5.1	3.22	0.001
Median (range)	7.5 (5–18)	11 (6–21)		

Z_{MWU}, Z value of Mann-Whitney U test.

The side effects of both groups were comparable (Table 3) even though 3 patients in group I discontinued the medication due to dizziness (2 patients of 3) and postural hypotension (1 patient). In group II, 4 patients discontinued the MET due to dizziness (2 patients of 4) and postural hypotension (2 patients). The pain episodes experienced by both groups were mild where the analgesic requirement (Table 4) was at a mean (SD) 193 ± 83.3 and 204.2 ± 95.1 mg in groups I and II, respectively, with no significant difference (p = 0.58). Concerning retrograde ejaculation, 10 and 5 patients of 43 and 41 patients in groups I and II, respectively, experienced this drawback with no significant difference between the 2 groups (p = 0.18).

While comparing stone size <6 mm there was significant statistical difference between the 2 groups regarding the analgesic requirement as it was mean (SD) 103.1 ± 55.8 vs. 206.2 ± 96.1 mg in groups I and II respectively (p = 0.017). Also, there was a significant difference in stone expulsion time as it was mean (SD) 6 ± 0.9 vs. 7 ± 0 days in groups I and II respectively (p = 0.01), but there was no statistical difference regarding the stone expulsion rate as it was 100% in both groups (Table 5).

Regarding stone size 6–10 mm, there was no significant difference between the 2 groups in analgesic requirement, as it was mean (SD) 206.2 ± 78.8 vs. 203.9 ± 95.8 mg between groups I and II, respectively (p = 0.75), while there was a significant difference in stone expulsion rate, as it was 80% (48 of 60) in group I and 56.1% (32 of 57) in group II. Also, a highly significant difference was present between the 2 groups regarding the stone expulsion time as it was mean (SD) 9.8 ± 3.8 vs. 14.1 ± 4.9 days in groups I and II respectively (p value <0.001; Table 5).

Table 3. Comparison between study groups regarding complications

Variable	Group I (n = 68)	Group II (n = 65)	p value
Dizziness, n (%)	3 (4.4)	4 (6.2)	0.65
Postural hypotension, n (%)	1 (1.47)	2 (3.1)	0.53
Headache, n (%)	1 (1.47)	1 (1.51)	0.97
Retrograde ejaculation*, n (%)	10 (23.3)	5 (12.2)	0.18

* In Group I out of 43 and in Group II out of 41.

Discussion

Stone disease is a chronic disorder with a high recurrence rate, as up to 50% of patients experienced additional colicky attacks within 5 years of their 1st episodes. So, it is a disease with great economic consequences [10, 11]. Many treatment modalities are adopted for the management of the DUS, comprising open ureterolithotomy, ureteroscopy, and shock wave lithotripsy [12]. However, these modalities are costly and not risk free [4].

Nowadays, MET is known as an alternative modality for the initial treatment of selected patients with DUS [13]. MET with relatively limited risks should be balanced against the natural course of ureteral stones without treatment. Several factors govern the management of ureteral stones as the type, location, size, number, structure of the stone, and whether symptomatic or not. Moreover ureteral spasm, inflammation, and ureteral anatomy influence stone expulsion [14, 15].

MET is usually established as an initial treatment plan of DUS of size 5–10 mm, as they are less likely to pass spontaneously [16]. Earlier studies stated that the rate of ureteric stone expulsion by watchful waiting is 25–54% with a mean expulsion time of more than 10 days accompanied by high analgesic requirement even for stones less than 5 mm, and so MET was instituted to improve the expulsion rate, reduce the expulsion time, and minimize analgesic requirement [16, 17].

In the distal ureter, the alpha 1A and alpha 1D are predominant, so blockade of these receptors minimizes the ureteric tone, lowers the peristaltic amplitude and frequency leading to decline in the intra-luminal pressure and increase in urine transport, so increasing the stone passage [18]. Our present study showed that the silodosin group had a significant statistical advantage in terms of the stone expulsion rate (82.4%) versus tamsulosin group (61.5%) for stones 5–10 mm (p = 0.007). Similar data to ours was found in the study done by Gupta et al. [19] who reported stone expulsion rates of 82 and 58% for their silodosin and tamsulosin groups respectively. Moreover our results are consistent with those of Kumar et al. [20] in which the stone expulsion rate was 83.3 and 64.4% for the silodosin and tamsulosin groups respectively. The difference regarding the stone expulsion rate was insignificant between silodosin (88%) and tamsulosin (84%) in study done by Imperatore et al. [21]. The stone expulsion rate diminished dramatically to 52% in the study done by Sur et al. [22] who studied the efficacy of silodosin in upper, middle, and lower ureteric stones, and this may be attributed to the fact that alpha 1 a adrenoceptors are more abundant in the lower ureter.

In regard to stone expulsion time, our results showed that the silodosin group exhibited better results over the tamsulosin group as it was 9.4 ± 3.8 and 12.7 ± 5.1 days for silodosin and tamsulosin groups, respectively, and the difference was statistically significant (p = 0.001). This may be explained by the selective alpha 1A adrenoceptive antagonistic action of silodosin when compared to alpha 1A antagonistic action of tamsulosin suggesting better clinical usefulness of silodosin. These results of the present study were comparable with studies done by Elgalaly et al. [23], Gupta et al. [19], and Kumar et al. [20] regarding the shorter stone expulsion time of silodosin over tamsulosin; however, the stone expulsion time in this study is shorter than these studies, and this may be attributed to the difference in patients and stone characteristics.

Interestingly Imperatore et al. [21] reported a shorter stone expulsion time than ours for both silodosin and tamsulosin groups as it was 7.9 and 7.7 days respectively. Ureterolithiasis causing ureteral colic accounts for up to 2% of the hospital emergency admission [19]. The increase in the intra ureteral pressure that occurs above the site of ureteral obstruction by the stone is the main etiology of ureteral colicky pain [20]. The alpha adreno-

Table 4. Analgesic requirement in both groups

Variable	Group I (n = 68)		Group II (n = 65)		Z_{MWU}	p value
	mean ± SD	median (range)	mean ± SD	median (range)		
Analgesic requirements	193±83.3	150 (75–375)	204.2±95.1	225 (75–375)	0.56	0.58

Z_{MWU}, Z value of Mann-Whitney U test.

Table 5. Analgesic requirement and outcome according to stone size among the studied groups

Variable	Group I (n = 8)		Group II (n = 8)		Test of significance	p value
	mean ± SD	median (range)	mean ± SD	median (range)		
Stone size <6 mm						
Analgesic requirements	103.1±55.8	75 (75–225)	206.2±96.1	187.5 (75–375)	Z_{MWU} = 2.38	0.017
Outcome, n (%)						
Passed	8	100.0	8	100.0	–	–
Not passed	0	0.0	0	0.0		
Stone expulsion time, days	6±0.9	6 (5–7)	7±0	7 (7–7)	Z_{MWU} = 2.57	0.01
Variable	Group I (n = 60)		Group II (n = 57)		Test of significance	p value
	mean ± SD	median (range)	mean ± SD	median (range)		
Stone size 6–10 mm						
Analgesic requirements	206.2±78.8	225 (75–375)	203.9±95.8	225 (75–375)	Z_{MWU} = 0.31	0.75
Outcome, n (%)						
Passed	48	80.0	32	56.1	χ^2 = 7.69	0.006
Not passed	12	20.0	25	43.9		
Stone expulsion time, days	9.8±3.8 (n = 48)	8.5 (5–18)	14.1±4.9 (n = 32)	12.5 (6–21)	Z_{MWU} = 3.67	<0.001

Z_{MWU}, Z value of Mann-Whitney U test.

ceptor blockers may alleviate the ureteric colic by blocking C fibers that mediates pain and decreases the analgesic requirements by decreasing the stone expulsion time [23].

In this study, the analgesic requirements are comparable in both silodosin and tamsulosin groups, as it was 193 ± 83.3 and 204.2 ± 95.1 mg respectively (p = 0.58) with no significant difference. Meanwhile, Kumar et al. [20] reported significant less analgesic requirement in the silodosin group versus the tamsulosin group, as it was 195 ± 10.2 and 220 ± 10.8 respectively (p = 0.000).

In our study we compared stone size <6 vs. 6–10 mm and found that in case of stones <6 mm, the stone expulsion rate was similar in both groups (100%), but the stone expulsion time and analgesic requirement were significantly less in group I than in group II. But for stones 6–10 mm, our study showed a significant advantage for silodosin over tamsulosin in stone expulsion rate and time but not for analgesic requirement. These results agree with Huang et al. [24] that showed the significance of silodosin in accelerating the expulsion of DUS 5–10 mm versus the control group.

Alpha 1 adrenoceptors are involved in the contraction of blood vessels. The alpha 1B adrenoceptor is the most abundant alpha 1 subtype in large vasculature. The blockage of that receptor is the main cause of side effects as headache, dizziness, and postural hypotension [25–27]. The expression of alpha 1A adrenoceptors increases with age and the ratio between alpha 1B: alpha 1A also increases [26]. Latest studies proved the advantage of silodosin over tamsulosin regarding the cardiovascular adverse effects due to its higher subtype selectivity [25].

In the present study, the encountered cardiovascular side effects (headache, dizziness, and postural hypoten-

sion) were mild and well tolerated except in 3 and 4 patients in groups I and II, respectively, as they discontinued the medications due these side effects and the statistical difference between groups I and II were insignificant. In that era, our results were similar to those of the studies done by Kumar et al. [20] and Imperatore et al. [21]. Retrograde ejaculation occurred in both groups with no significant difference, as it was reported in 10 (23.3%) and 5 (12.2%) patients in the silodosin and tamsulosin groups, respectively (p = 0.18), but no patients in any group discontinued the medication. On the contrary, Imperatore et al. [21] reported a significant difference between silodosin (2%) and tamsulosin (8%) groups regarding retrograde ejaculation.

Conclusion

In conclusion, the safety of both drugs is comparable, but the efficacy shows better results for silodosin regarding stone expulsion time and rate, but the patients need psychogenic support regarding disturbed ejaculation that is more with silodosin. Financial issues for the patients are important and, in this study, we recommend that MET be considered the 1st line of treatment in uncomplicated stone lower 3rd ureter 10 mm or less.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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