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Comparison of Silodosin, Tadalafil and Combinations Prior to Ureteroscopic Management of Ureteral Stones

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ABSTRACT
The present paper, aims to assess and compare the therapeutic efficacies of silodosin, Tadalafil, and their combination for the negotiation of large semi-arid ureteroscopic through ureteric orifice during ureteral stone management. During endoscopy, the patients in groups A, B, and C exhibited wider ureteric orifice than the patients of group D. About 70.6%, 60.6%, 62.9% and 32.4% of patients belonging to groups A, B, C, and D, respectively, exhibited easy negotiation. Significantly lower proportions of patients in groups A, B, and C (35.3%, 39.4%, and 28.6%, respectively) exhibited the need for ureteral dilation compared to those in group D (61.8%). In addition, the duration of surgery for groups A, B, and C was less than that for group D. Preoperative silodosin and Tadalafil administration in patients undergoing ureteroscopic for ureteral stones improves the access of large size duretero scope and reduced the need for ureteral dilatation with less surgical duration and minimal adverse events.

Keywords: Tadalafil; silodosin; ureteroscopic; ureteral stone; alpha blockers; urolithiasis

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INTRODUCTION
Ureteral stone is a common urological condition with incidences of 12% and 6% in males and females, respectively [1]. Several studies have shown successful management of distal ureteric stones using semi-rigid ureteroscopic (URS) [2-3]. However, there are certain drawbacks tours [4]. The narrowness of the ureterovesical junction (UVJ) poses a difficulty in spontaneous expulsion of the stone and negotiation of ureteroscopic [5-6].Negotiation through UVJ is a crucial aspect of ureteroscopic. Several patients undergoing ureteroscopic need ureteric orifice dilation during employment of a large-sized ureteroscopic (8/9.8 Fr) [7]. Researchers have reported that phosphodiesterase inhibitors (PDE 5i) and alpha blockers participate in the expulsion of ureteric calculi. Entire ureteral wall is lined with alpha-adrenergic receptors; however, they are majorly localized to the lower portion of the ureter. PDE 5i are involved in up regulation of cGMP via the nitric oxide/cGMP signaling pathway. Up regulation of cGMP leads to relaxation of ureteral smooth muscle [8-9]. Antagonism of alpha adrenergic receptors decreases ureteral spasm and relaxes the smooth muscles of the ureter, which promotes calculi expulsion [10-11]. Recently, there has been increased interest in their potential role in facilitating ureteroscopic and instrumentation of the ureter based on the same pharmacological effects utilized for medical expulsive therapy. Technical studies have supported the use of alpha blockers used before ureteroscopic by facilitating deployment of ureteral access sheaths without increasing ureteralinjuries [12].

METHODS
We recruited 136 individuals between the ages of 18 to 70 years, who harbored a single, uncomplicated calculus (6–18 mm) in the ureter. The exclusion criteria included infection, fever, moderate to gross hydronephrosis, bilateral or multiple calculi, chronic or acute renal insufficiency, congenital urinary abnormality, solitary kidney, history of endoscopic interventions or open surgery, pregnant or lactating mothers, or undergoing treatment with alpha- and beta-blockers, steroids, nitrates, or calcium antagonists. We also excluded patients who demanded immediate intervention and exhibited spontaneous calculi expulsion. The recruited patients were divided into Groups A (once daily administered with 8 mg silodosin), B (once daily administered with 5 mg Tadalafil), C (once daily administered with 8 mg silodosin and 5 mg Tadalafil), and D (placebo).Drug administration was commenced 7 days before the surgery. Each patient's medical history was recorded, and all patients underwent physical examination. We also recorded the patient characteristics, such as gender, age, and location and size of the stone. Here, the largest dimension of the stone was considered as the stone size. The patients also underwent serum creatinine analysis, ultrasonography, urinalysis, computed tomography (CT), and X-ray of the kidneys, ureter, and bladder (KUB) prior to the surgery. . All the patients underwent X-ray KUB and ultrasonography to check for any residual fragment. The follow-up period was 4 weeks, postoperatively.

Surgical procedure
The patients were laid in lithotomic position and administered spinal anesthesia. Their bladder, urethra, and ureteric orifice were examined via cystourethroscopy. The width of the ureteric orifice was recorded before insertion of a 0.035 Fr guide wire. Next, we attempted insertion of 8/9.8 Fr wolf ureteroscopic over the guide wire. We considered the protocol as complete if the ureteroscopic could be inserted easily without any maneuver. In case of difficult insertion, the orifice was dilated to 10 Fr using a ureteral dilator; then, the ureteroscopic was inserted, and the calculus was removed using dormia basket, grasper, or laser lithotropy. Later, a double J stent was placed inside all the patients (according to the institution's protocol). Only a

senior urologist performed the ureteroscopic as well as cystoscopy. For all the patients, we recorded the configuration of the orifice, type of negotiation, need for dilatation, and duration of surgery, complications (including fever, false passage /mucosal injury, and hematuria), drug-related side effects, and stone-free rate.

RESULTS

One hundred and thirty-six patients were recruited for this study. We divided the patients into four groups based on the drug administered: A (silodosin), B (Tadalafil), C (silodosin + Tadalafil), and D (placebo). No significant differences were observed among the patients' characteristics (gender, age, stone location and size, etc., table 1). The intra-procedural patient characteristics are shown in Table 2.For groups A, B, and C, the number of patients who showed a wide ureteric orifice was significantly high compared to those in group D (75.35%, 66.7%, and 77.1% vs. 20.6%; p = 0.00001, 0.0001, and 0.00001, respectively). However, the difference in the number of patients with a wide orifice between groups A, B, and C was not statistically significant. Similarly, for groups A, B, and C, the number of patients who exhibited easy negotiation of the orifice was significantly higher than those in group D (24 (70.6%), 20 (60.6%), and 22 (62.9%) vs. 11 (32.4%); p = 0.002, 0.02, and 0.01, respectively). Furthermore, the number of patients in groups A, B, C, and D who required ureteral dilatation was 12 (35%), 13 (39.4%), 10 (28.6%), and 21 (61.8%). The number of patients of groups A and C who needed ureteral dilatation were significantly less than those in group D (p = 0.03 and 0.06, respectively). Moreover, there was no significant difference between groups A, B, and C. The mean duration of surgery for group A, B, and C patients was significantly less than that for patients of group D (37.41, 37.48, and 37.82 min vs. 43.08 min, respectively). However, there were no significant differences between groups A, B, and C(Table 3). The stone-free rates and the need for postoperative analgesia were not significantly different among any of the groups (Table 4). As shown in Table 5, significantly higher number of patients belonging to groups B and C experienced dyspepsia, headache, and backache compared to groups A and D ($P< 0.05$). On the contrary, more patients of groups A and C complained of abnormal ejaculation and dizziness than those of groups B and D ($P> 0.05$). Hematuria was presented in 6, 7, 6, and 11 patients; mucosal injury was observed in 4, 5, 5, and 10 patients; and post-operative fever was exhibited by 5, 4, 5, and 6 patients in groups A, B, C, and D, respectively. However, there were no significant differences in the number of patients who presented with procedural complications among any of the groups (Table 6).

Table 1: Patients' and stone characteristics

Parameter	Group A	Group B	Group C	Group D	P value
Number	34	33	35	34	
Age (years) (mean ± SD)	33.29±9.51	32.96±10.42	34.42±11.63	34.60±12.01	0.9
Sex (Male/Female)	25/9	23/10	25/10	25/9	0.07
Side (left/right)	18/17	15/18	16/19	17/17	0.9
Location of calculus (upper/middle/lower)	3/6/25	4/5/24	4/6/25	3/6/25	0.07
Size (mm) (mean ± SD)	10.35±2.38	10.24±2.12	10.37±2.47	10.41±2.43	0.99

Table 2: Perioperative characteristics and outcome

Variables	Group A (N = 34) No.(%)	Group B (N = 33) No.(%)	Group C (N = 35) No.(%)	Group D (N = 34) No.(%)	P value
Configuration of the orifice					0.00001
Narrow	9 (26.5%)	11 (33.3%)	8 (22.9%)	27(79.4%)	
Wide	25 (73.5%)	22 (66.7%)	27 (77.1%)	7 (20.6%)	
Negotiation of ureteric orifice by ureteroscopic					0.009
Difficult	10 (29.4%)	13 (39.4%)	13 (37.1%)	23(67.6%)	
Easy	24 (70.6%)	20 (60.6%)	22 (62.9%)	11(32.4%)	
Ureteral dilation					0.03
required	12 (35.3%)	13(39.4%)	10 (28.6%)	21 (61.8%)	
Not Required	22 (64.7%)	20(60.6%)	25 (71.4%)	13 (28.2%)	
Mean operative time (min)	37.41±3.09	37.48±3.33	37.82±2.13	43.08±3.07	0.000

Table 3: Statistical comparison between the groups

Variables	A vs. B	A vs. c	A vs. D	B vs. c	B vs. D	C vs. D
Configuration of the orifice	0.5	0.7	0.00001	0.3	0.0001	0.00001
Negotiation through orifice	0.4	0.5	0.002	0.8	0.02	0.01
Need of ureteral dilatation	0.7	0.5	0.03	0.3	0.07	0.006
Mean duration of surgery (min)	0.9	0.5	0.0001	0.6	0.0001	0.0001

Table 4: Perioperative and postoperative data

Variable	Group A (*N* = 34) No. (%)	Group B (*N* = 33) No. (%)	Group C (*N* = 35) No. (%)	Group D (*N* = 34) No. (%)	P value
Stone-free rate, n/N (%) At 24–48 h	30 (88.2%)	29 (87.9%)	31 (88.6%)	26 (76.5%)	0.4
After 4 weeks	32 (94.1%)	30 (90.9%)	33 (94.3%)	28 (82.4%)	0.3
Need for analgesia, n (%)	6 (17.6%)	5 (15.2%)	4 (11.4%)	9 (26.5%)	0.4

Table 5: Drug-related side-effects

	Group A (*N* = 34) No. (%)	Group B (*N* = 33) No.(%)	Group C (*N* = 35) No.(%)	Group D (*N* = 34) No.(%)	P-value
Headache, backache	5 (14.7%)	13 (39.4%)	11 (31.4%)	4 (11.8%)	0.02
Dyspepsia	4 (11.8%)	11 (33.3%)	12 (34.3%)	5 (14.7%)	0.04
Abnormal ejaculation	5 (14.7%)	2 (6.1%)	4 (11.4%)	1 (2.9%)	0.3
Dizziness	5 (14.7%)	4 (12.1%)	6 (17.1%)	4 (11.8%)	0.9

Table 6: Complications due to the procedure

Outcome variables	Group A (silodosin) *N*=34	Group B (Tadalafil) *N*=33	Group C (silodosin +Tadalafil) *N* =35	Group D (placebo) *N*=34	P-value
Hematuria	6 (17.6 %)	7 (21.2 %)	6 (17.1%)	11 (32.4 %)	0.4
Mucosal injury	4 (11.8%)	5 (15.2 %)	5 (14.3 %)	10 (29.4 %)	0.2
Fever	5 (14.7%)	4 (12.1 %)	5 (14.3%)	6 (17.6%)	0.9

DISCUSSION

Selection of an ideal ureteric stone removal technique largely depends on the patient's preferences, stone characteristics (size, type, position, obstruction, and degree of impaction), and the experience and skills of the surgeon [13-14]. However, ureteroscopic is currently the most preferred approach for most cases [15].The 2016 American Urological Association guidelines recommend administration of alpha-blockers and MET for ureteral calculi management[16]. The European Association of

Urology guidelines report medical expulsive therapy as effective when administered after ureteroscopic; however, it does not mention preoperative use of alpha-blockers [16]. Failure to access the ureter has been reported to be in the range of 8–10% [17].Dilatation is usually needed to navigate a tight ureter or orifice and is associated with complications [18]. Preoperative alpha-blockers may be most effective for larger ureteroscopic sizes, given the increased degree of ureteral relaxation required to facilitate a larger ureteroscopic. In addition, they might be beneficial for distal ureteral stones causing ureteral orifice edema, inflammatory changes, and/or ureteral spasm, which might hinder ureteroscopic. Majority of previous studies have reported administration of alpha-blockers for 1 week before ureteroscopic [19-21]. The ureteric orifice is present in the UVJ, which is the narrowest part of the ureter and poses a challenge for the urologist to insert the ureteroscopic through it, which is a vital part of ureteroscopic. The use of a smaller-sized ureteroscopic could facilitate the process, but it could also compromise the stone-removal efficacy and visibility. In contrast, a large-sized ureteroscopic would require dilatation of the orifice [22-23]. The difficult negotiation through the orifice can be rectified using several approaches, such as active (metal, olives, balloon, etc.) or passive (double J stent) dilatation; however, these approaches accompany their own complications [22-24]. Most of the adrenergic receptors present in the ureter arealpha-1 A- and D-adrenergic receptors. Most of these receptors are located in the lower portion of the ureter [9,11]. Gratzke et al. showed that PDE-5i selectively bound with Tadalafil without any visible side effects [8,25]. Hence, we used lower concentration of Tadalafil in this study. We observed a significantly longer mean duration of surgery for patients of group D, which could be attributed to the dilatation requirement of most of group D patients. The time taken for dilatation of the orifice and negotiation of the ureteroscopic increased the overall surgical duration. Several studies have shown ureteral relaxation and better ureteroscopic negotiation in patients administered with Tadalafil and silodosin [26-28]. We observed similar results. Overall, 25 (73.5%), 22 (66.7%), and 27 (77.1%) patients of groups A, B, and C, respectively, exhibited dilated orifice. Negotiation was easier for 24 (70.6%), 20 (60.6%), and 22 (62.9%) patients of the three groups, respectively. On the contrary, only 7 (20.6%) patients of group D showed dilated orifice, and only 11 (32.4%) patients presented ease of negotiation. Previously, Aydin et al., [29] reported that silodosin administration prior to URS led to a higher rate of access to the calculi with reduced complications. This supports the previous findings that the alpha-adrenergic receptor blocking causes relaxation of ureteral smooth muscle and reduction in the frequency and force of peristalsis [11,30]. Our results indicated that, among the four groups, most patients that presented with complications belonged to group D. The most common complications in group D patients were hematuria and mucosal injury. Most of the drug-related side-effects, including backache, dyspepsia, and headache, were observed in the patients administered with Tadalafil. The limitations of present study included small sample size and single-center study, which led to potentially subjective findings with respect to orifice configuration and negotiation. We did not record the configuration of the orifice before the drug administration, which further made our assessment subjective. In conclusion, preoperative silodosin and Tadalafil use in patients undergoing ureteroscopic for ureteral stones improves access of large size ureteroscopic and reduced the need for ureteral dilatation with less operative time and without any significant risk of adverse events.

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