ISSN : 0974 - 7435 Volume 12 Issue 3

BioTechnology
An Indian Journal

FULL PAPER

BTAIJ, 12(3), 2016 [136-144]

Oral silodosin on lower urinary tract symptoms due to double-j stent: a prospectively randomized study

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ABSTRACT

Introduction: To evaluate the effect of silodosin in improving symptoms and quality of life in patients with indwelling double-J ureteral stents, using a specific questionnaire.

Experiments: One hundred sixty-one patients with symptomatic distal ureteral stones <15 mm diameter were enrolled. In group 1, 78 patients received a placebo (lactose tablet) for two weeks. In group 2, 83 patients received 4 mg of silodosin once daily before bed for two weeks. All patients completed the validated ureteral stent symptom questionnaire (USSQ) and International Prostate Symptom Scale (IPSS) for quality of life for evaluating the symptoms of double-J stents and quality of life after double-J stent insertion and removal, respectively. Statistical analysis was performed using the chi-square test, Mann-Whitney U test, and Fisher's exact test, as appropriate.

Results: One hundred sixty-one patients completed the study. No significant statistical difference was observed in patient age, gender distribution, body height, stone size, or operative times ($p>0.005$). The mean urinary symptom index was significantly less ($p<0.001$) in group 2 patients. Stent-related pain was similar in both groups, but the overall intensity as identified on the visual analog scale was more severe in group 1 patients ($p<0.001$). General health scores were significantly greater in group 1 patients, leading to significant ($p<0.001$) interference with their lives related to the presence of the stent. The mean score of IPSS quality of life was 4.18±0.79 in group 1 and 1.57±0.68 in group 2.

Conclusion: The administration of silodosin improves stent-related urinary symptoms, pain, and voiding flank pain.

KEYWORDS

Silodosin;
Double-J stent;
USSQ;
LUTS;
Alpha-1 blocker.

INTRODUCTION

The placement of a ureteral stent is a common urological intervention. It has been more than three decades since the first description of a cystoscopically placed temporary ureteral stent by Zimskind et al., [1] and its indications and use have continued to expand[2]. However, the side effects and

patient morbidity associated with ureteral stents have been identified as a potential health problem[3]. The great variety of complications range from the commonly experienced "stent syndrome" to the medicolegal dilemma of the forgotten stent[4].

The assessment of stent-related urinary symptoms is not easy when using common clinical measures. Joshi et al. presented validated questionnaires for the assessment of stent-related symptoms and the evaluation of their impact on patients' daily life[5]. This questionnaire may have levels of precision that exceed those of clinical measures. Moreover, most efforts have been aimed toward improving stent materials and design. Few papers mentioned the resolution of troublesome symptoms. Recently, Deliveliotis et al. reported that the administration of afluzosin improved stent-related urinary tract symptoms and pain[6]. They hypothesized that a selective alpha-1 blocker might influence stent-related symptoms, because the latter mimics the lower urinary tract symptoms due to benign prostatic hyperplasia. Silodosin is a newly potent selective α-1A specific blocker that is well-tolerated and clinically effective in improving symptoms and urinary flow rate in patients with symptomatic benign prostatic hyperplasia [BPH][7]. Therefore, a randomized double-blind controlled study was conducted to evaluate the effect of silodosin in improving symptoms and quality of life in patients with indwelling double-J ureteral stents, using a specific questionnaire.

EXPERIMENTS

Our Institutional Review Board of St. Martin De Porres Hospital in Chia-Yi city, within which the work was undertaken, gave permission to do the study. All procedures performed in studies involving human participants were done in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients signed an informed consent form before participating. To detect a 30% difference in the proportion of stent-related complications in the treatment groups at a significance level of 0.05 and a power of 90%, a sample size of 75 patients per group was calculated. All patients, with the insertion of a double-J ureteral stent after ureteroscopic stone removal, were prospectively randomized (using a random numbers table) into two groups.

From November 2011 to April 2014, all patients with symptomatic distal ureteral stones <15 mm diameter, removed completely by ureteroscope, were enrolled in this prospective study. All patients completed the validated ureteral stent symptom questionnaire (USSQ) and International Prostate Symptom Scale (IPSS) for quality of life for evaluating the symptoms of double-J stents and quality of life after double-J stent insertion and removal, respectively. Since the USSQ and IPSS were adapted and translated in Chinese, medicines were administered one week after their first evaluation. Another questionnaire was administered two weeks after stent removal as a baseline study. We expected that, at two weeks after stent removal, symptoms would have completely subsided. Thus, the questionnaire administration at that time would have been representative of the baseline urinary symptoms, having nothing to do with ureteral calculi and ureteroscopic manipulation itself. Statistical analysis was performed using the chi-square test, Mann-Whitney U test, and Fisher's exact test, as appropriate.

The exclusion criteria included benign prostatic hyperplasia-related lower urinary symptoms (IPSS score greater than 7); a history of interstitial cystitis, chronic cystitis, chronic prostatitis, or stent insertion; and chronic medication with alpha blockers or analgesics. During the stenting period, all patients were prescribed Pipemic acid trihydrate 250 mg twice per day to minimize urinary tract infections, and allowed to use sublingual buprenorphine 0.2 mg on demand; overall dosage was documented and compared. The same double-J ureteral stent design, consisting of an all-silicone coating (Cliny, Japan), was inserted in all patients. The stent size was fixed (Fr 7) and the length was adjusted by body height, applied to all patients after ureteroscopic stone removal under intravenous general anesthesia, and its correct position relative to the status of stones was confirmed with a plain kidney-ureter-bladder x-ray.

FULL PAPER

The double-J stents were removed by cystoscopy two weeks later. All consenting patients were fully informed regarding the potential side effects of silodosin; however, they were unaware of whether they were receiving a placebo or silodosin. Also, the physician who administered the medication was unaware of the treatment arm of the patients.

RESULTS

Two hundred twenty-four patients were eligible and prospectively randomized into two groups. In the control group, a total of 95 patients were available for consideration. Among them, seven patients did not meet the inclusion criteria and six patients refused the consent; they were eliminated from the study. In group 1, 82 patients (60 male and 18 female) (mean age 51.63 years old) were enrolled; they received a placebo (lactose tablet) for two weeks. In the silodosin group, a total of 101 patients were available. Among them, seven patients did not meet the inclusion criteria and seven patients refused consent; they were eliminated from the study. Thus, a total of 87 patients were enrolled and received silodosin treatment. Four patients per group eventually did not receive the allocated treatment due to loss to miss primary outcome after randomization. Thus, analysis was done with 78 and 83 patients as the denominator in each randomization arm (Figure 1). One hundred sixty-one patients completed the study. No significant statistical difference was observed in patient age, gender distribution, body height, stone size, or operative times (p >0.005) (TABLE 1). No complications occurred after double-

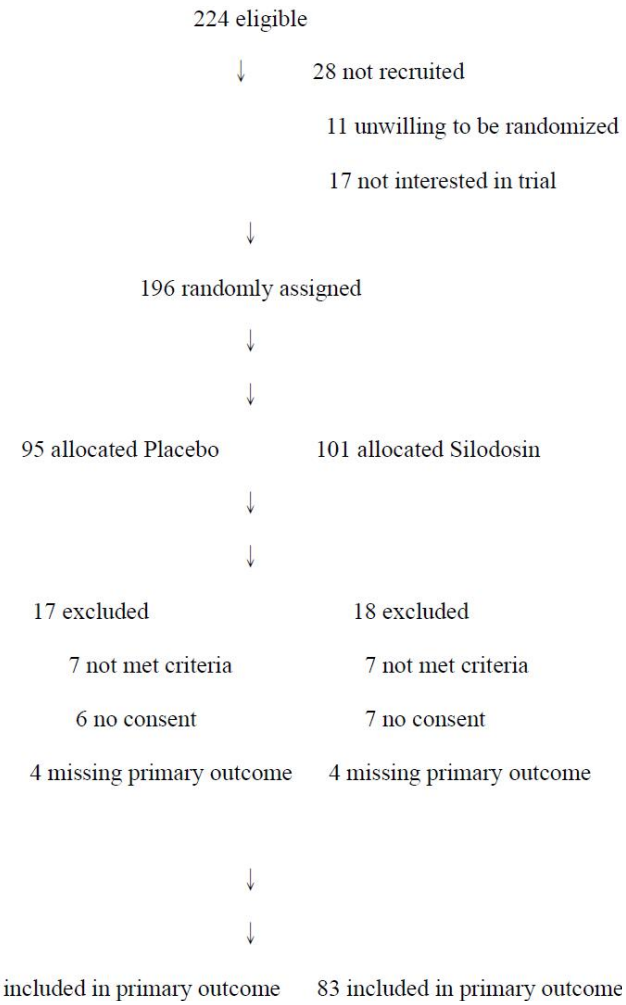

Figure 1 : Summary of study disposition, Numbers of participants declining further follow-up or not responding are cumulative in direction of participant flow

TABLE 1 : Patients characteristics

Characteristic	Placebo	Silodosin	*P* value
	N=78	N=83	
Age(yr) [a]			0.643
Mean	51.63 ± 10.88	50.41 ± 9.70	
Range	29-79	28-76	
Gender [b]			0.832
Male	60 (76.92)	65 (78.31)	
Female	18 (23.08)	18 (21.69)	
IPSS before trial [a]	2.51 ± 1.69	2.58 ± 1.68	0.774
Male <50 y/o [a]	1.33 ± 1.07	1.46 ± 1.17	0.413
Male =50 y/o [a]	3.70 ± 1.31	3.57 ± 1.20	0.833
Female <50 y/o [a]	1.10 ± 0.88	1.57 ± 0.79	0.238
Female =50 y/o [a]	3.38 ± 1.60	4.45 ± 1.44	0.116
Body mass index [a]	25.21 ± 2.66	24.94 ± 2.74	0.558
Male [a]	25.11 ± 2.46	24.98 ± 2.71	0.681
Female [a]	25.56 ± 3.31	24.80 ± 2.92	0.590
Stone sizes(mm) [a]	6.55 ± 1.38	6.66 ± 1.42	0.790
Operative times(mins) [a]	33.28 ± 5.66	37.28 ± 6.64	< 0.001
Employment Status [c]			0.710
Full time	52 (66.67)	49 (59.04)	
Part time	15 (19.23)	17 (20.48)	
Retired	8 (10.26)	12 (14.46)	
Others	3 (3.85)	5 (6.02)	
Sexually active [b]	32 (41.0)	32 (38.55)	0.749

Values are presented as mean±standard deviation or number (%); ***p < 0.001; [a] Mann-Whitney U test; [b] chi-square test; [c] Fisher's exact test

TABLE 2 : Randomization study results

Varible	Placebo	Silodosin	*P* value [a]
Urinary Symptoms			
W1 mean index score	31.38 ± 4.80	20.82 ± 3.37	< 0.001***
Male <50 y/o	30.93 ± 4.46	21.11 ± 3.31	< 0.001***
Male =50 y/o	31.85 ± 4.34	20.64 ± 3.05	< 0.001***
Female <50 y/o	30.50 ± 6.29	20.43 ± 3.05	0.005**
Female =50 y/o	32.13 ± 6.20	20.55 ± 4.72	0.000***
W4 mean index score	15.09 ± 1.99	15.30 ± 2.09	0.458
Male <50 y/o	14.78 ± 1.60	15.59 ± 2.05	0.089
Male =50 y/o	15.09 ± 2.14	15.14 ± 1.86	0.930
Female <50 y/o	15.10 ± 2.08	15.00 ± 1.53	0.796
Female =50 y/o	16.13 ± 2.42	14.91 ± 3.05	0.238
Body Pain(patients)			
W1 mean sum VAS	5.68 ± 1.17	3.88 ± 0.95	< 0.001***
W1 mean index score	13.51 ± 13.30	9.81 ± 9.64	0.020*
Male <50 y/o	8.89 ± 11.90	8.76 ± 9.48	0.960
Male =50 y/o	16.88 ± 13.17	11.07 ± 9.41	0.011*
Female <50 y/o	10.60 ± 13.89	11.14 ± 11.70	0.962
Female =50 y/o	18.88 ± 14.03	9.27 ± 10.34	0.091
W4 mean index score	3.91 ± 3.84	3.99 ± 4.13	0.967
Male <50 y/o	4.30 ± 4.07	3.95 ± 4.14	0.645
Male =50 y/o	3.70 ± 3.67	3.50 ± 3.76	0.813
Female <50 y/o	3.00 ± 3.16	5.00 ± 5.13	0.536
Female =50 y/o	4.63 ± 4.87	4.73 ± 4.69	1.000
Gereral Health			
W1 mean index score	12.12 ± 2.98	10.08 ± 2.27	< 0.001***
Male <50 y/o	12.07 ± 2.76	9.97 ± 2.34	< 0.01**
Male =50 y/o	11.88 ± 2.32	9.82 ± 2.21	< 0.01**
Female <50 y/o	12.00 ± 3.62	10.86 ± 1.77	0.669
Female =50 y/o	13.38 ± 5.07	10.64 ± 2.54	0.238
W4 mean index score	9.55 ± 3.09	8.22 ± 1.46	< 0.001**
Male <50 y/o	10.04 ± 2.81	8.27 ± 1.52	< 0.001**
Male =50 y/o	9.24 ± 2.51	8.04 ± 1.67	< 0.05**
Female <50 y/o	8.90 ± 3.51	8.29 ± 0.76	0.887
Female =50 y/o	10.00 ± 5.35	8.45 ± 1.04	0.904
Work Performance			
Mean days in bed	1.69 ± 0.96	1.48 ± 0.72	0.148
Mean of days with lost activity	1.50 ± 0.91	1.49 ± 0.82	0.967
W1 mean index score	11.95 ± 2.81	10.93 ± 2.28	0.017*
Male <50 y/o	12.00 ± 2.18	11.05 ± 2.17	0.073
Male =50 y/o	11.94 ± 3.36	10.36 ± 2.15	0.042*
Female <50 y/o	11.70 ± 2.45	10.00 ± 2.38	0.270

FULL PAPER

Varible	Placebo	Silodosin	*P* value [a]
Female =50 y/o	12.13 ±3.14	12.55 ± 2.30	0.717
W4 mean index score	6.96 ± 1.67	7.17 ± 1.67	0.352
Male <50 y/o	7.15 ± 1.61	7.24 ± 1.64	0.658
Male =50 y/o	6.97 ± 1.86	6.61 ± 1.29	0.583
Female <50 y/o	6.80 ± 1.40	7.00 ± 1.92	0.962
Female =50 y/o	6.50 ± 1.51	8.45 ± 1.97	0.041*
Sexual performance			
W1 mean index score	4.46 ± 3.13	4.34 ± 3.13	0.717
Male <50 y/o	3.48 ± 2.76	4.00 ± 2.97	0.356
Male =50 y/o	4.94 ± 3.04	4.00 ± 2.52	0.215
Female <50 y/o	5.60 ± 4.17	3.86 ± 2.48	0.475
Female =50 y/o	4.38 ± 2.88	6.64 ± 4.57	0.351
W4 mean index score	4.58 ± 2.32	4.94 ± 2.99	0.810
Male <50 y/o	4.30 ± 2.22	4.59 ± 2.89	0.876
Male =50 y/o	4.64 ± 2.00	4.61 ± 2.42	0.737
Female <50 y/o	4.90 ± 3.51	4.29 ± 2.36	0.887
Female =50 y/o	4.88 ± 2.53	7.36 ± 4.03	0.206
Additional Problems	12.85 ± 2.91	10.24 ± 4.93	< 0.001***
Male <50 y/o	12.56 ± 2.61	9.46 ± 4.53	< 0.05**
Male =50 y/o	12.82 ± 2.77	10.89 ± 4.72	0.143
Female <50 y/o	13.30 ± 3.89	11.43 ± 5.56	0.417
Female =50 y/o	13.38 ± 3.50	10.45 ± 6.50	0.091
Feeling of suffering from UTI	2.09 ± 0.96	2.05 ± 0.99	0.948
Need for antibiotic intake	1.91 ± 0.86	2.05 ± 0.99	0.329
Need for professional assistance	1.73 ± 0.75	2.05 ± 0.99	0.024*
Need to visit hospital	1.53 ± 0.60	2.05 ± 0.99	< 0.001***
Future another stent	5.59 ± 1.05	2.05 ± 0.99	< 0.001***
Quality of Life	4.18 ± 0.79	1.57± 0.68	?????
Buprenorphine dosage	0.09 ± 0.15	0.01 ± 0.04	< 0.001***
Male <50 y/o	0.04 ± 0.10	0.02 ± 0.06	0.205
Male =50 y/o	0.15 ± 0.19	0	< 0.001***
Female <50 y/o	0.04 ± 0.08	0.03 ± 0.08	0.887
Female =50 y/o	0.08 ± 0.10	0	0.177

Values are presented as mean ± standard deviation; *p < 0.05, **p < 0.01, ***p < 0.001; [a] Mann-Whitney U test

J stent placement.

The overall results are detailed in TABLE 2. The analysis of the questionnaire at week 1 revealed a significant difference in the main score index of urinary symptoms and general health and quality of life in IPSS score between groups 1 and 2. When performing the week4 evaluation, there was no significant difference in all domain scores between groups 1 and 2. In the analysis of different time periods, when comparing the week 1 evaluation with that of week 4 after double-J removal, both groups showed significant worsening of urinary symptoms, body pain, general health, and work performance, except sexual performance.

The mean urinary symptom index was significantly less (p<0.001) in group 2 patients. All the

urinary symptoms were present significantly less ($p<0.001$) in group 2. Stent-related urinary symptoms were considered significantly more of a problem in patients not taking the alpha-1 blocker.

Stent-related pain was similar in both groups, but the overall intensity as identified on the visual analog scale was more severe in group 1 patients ($p<0.001$). At W1, pain developed in the flank region in 12 group 1 patients and 13 group 2 patients; pain was noted in the groin area in six patients each from both groups; nine patients each reported pain in the bladder area in both groups. However, the mean pain index was not significantly less in patients taking silodosin ($p<0.001$, 3.88±0.95 versus 5.68±1.17). General health scores were significantly greater in patients not receiving the alpha1 blocker, leading to significant ($p<0.001$) interference with their lives related to the presence of the stent. However, patients taking the alpha-1 blocker (group 2) had significantly less difficulty in performing heavy activities ($p<0.001$), were not tired ($p<0.001$), were calmer ($p=0.01$), and enjoyed their social lives more ($p>0.001$). They rarely required extra help from their family or friends ($p<0.001$).

The days off work were similar ($p=0.967$; 1.50±0.91 days versus 1.49±0.82 days in groups 1 and 2, respectively), and the quality of work, described by the number of rests, job efficiency, and regular hours of work, did not differ among the two study groups and was not severely impaired ($p=0.148$). A similar percentage of patients was reported to be sexually active in both groups (42.6% and 40.5% for groups 1 and 2, respectively, $p=0.85$). Among these patients, the difference in the mean sexual matters score was not statistically significant (4.46±3.13 versus 4.34±3.13 in groups 1 and 2, respectively, $p=0.717$), with patients receiving silodosin reporting less pain during intercourse and being more satisfied with their sex lives without statistical significance. Feelings toward future repeat stenting were better in patients receiving silodosin than in patients receiving the placebo; this difference reached statistical significance (2.04 versus 5.57 in groups 2 and 1, respectively, $p<0.001$).

The mean quality of life score in IPSS was 4.18±0.79 in group 1 and 1.57±0.68 in group 2. Only five patients in the silodosin group experienced adverse effects associated with the medical therapy (transient hypotension, asthenia, syncope, palpitations, and retrograde ejaculation), whereas no patients suspended medical therapy, and the adverse effects disappeared. The mean dosage of buprenorphine was 0.09±0.15 in group 1 and 0.01±0.04 in group 2. Only 4 patients in group 2 needed sublingual buprenorphine therapy, whereas 25 patients in group 1 required such regimens and 9 patients suffered from adverse effects (dizziness, anorexia, and vomiting); a statistically significant difference was noted ($p<0.001$).

DISCUSSION

Indwelling double-J ureteral stents have become routine in the management of a variety of urinary tract diseases. Stents prevent urinary tract obstruction, divert urine, allow for faster tissue healing, dilate the ureter, and assist in stone passage[2]. However, the ideal stent is not yet available[3,4,8]. Many patients will experience significant stent-related morbidity, and an additional procedure to remove the stent is usually needed[3,9]. To minimize the above-mentioned problems[10], new double-J stents with tapered distal ends made from hydrophilic materials have been developed, and stents created from new biodegradable or tissue-engineered materials may eliminate the need for stent removal in the future[11,12]. Although most efforts have been directed toward improving stent material and design, little data are available regarding possible pharmacological management of stent-related morbidity.

This study was conducted to evaluate the role of selective alpha-1A blockers for the improvement of stent-related symptoms with double-J ureteral stents. This hypothesis was based on the similarity of stent-related symptoms to benign prostatic hyperplasia-related symptoms, which can now be reliably recorded by USSQ. In our study, the selected medication was extended-release silodosin hydrochloride, which is the most recently approved selective alpha-1A adrenergic receptor antagonist[13].

Because of its distinct pharmacology, silodosin has been reported to have relatively greater phar-

macologic selectivity for prostatic and urethral tissue vs vascular tissues than other currently available alpha-1 blockers. Silodosin acts as a competitive antagonist of alpha-1A adrenoceptor-mediated contraction of prostatic, bladder, and proximal urethral smooth muscle[14,15]. Consequently, urethral pressure and resistance, bladder outlet resistance, bladder instability, and relevant symptoms associated with benign prostatic hyperplasia are reduced. Studies have suggested a beneficial effect of silodosin on the quality of life in patients with benign prostatic hyperplasia. The once-daily formulation of silodosin has been developed to improve the convenience of dosing and to provide optimal pharmacokinetic coverage during a 24-hour period[16]. Moreover, as Itoh reported, human ureter α-1A and 1D adrenergic receptors are the most commonly expressed subtypes in real-time reverse transcription polymerase chain reaction and immunohistochemical staining[17], and α-1A adrenergic receptors are the main participants in phenylephrine-induced ureteral contraction in the human isolated ureter[18]. They found that the selectiveα-1A adrenergic receptors antagonist silodosin was more effective than the selective α-1D adrenergic receptors antagonist BMY-7378 for noradrenaline-induced contraction in the human ureter[19]. Thus, silodosin could relieve the irritation from indwelled ureteral stents.

Joshi et al[5,20,21] were the first to develop and assess the USSQ, suggesting that it has satisfactory validity with good evaluative and discriminate properties. The authors reported bothersome urinary symptoms and stent-related pain in 80% of patients, with storage symptoms and incontinence the symptoms mostly affecting quality of life. Also, in the same study, as much as 40% of patients experienced sexual dysfunction[21]. Our results regarding the controls are in accordance with their findings. In fact, 66% of the patients receiving the placebo reported stent-related pain. In this group of patients, frequency, urgency, pain during voiding, impaired sexual matters, and general health index scores developed apparently. Patients in group 1 (placebo) were less capable of performing heavy activities and had pain during intercourse, decreasing their overall satisfaction.

As shown in the study, the use of silodosin alleviated stent-related urinary symptoms. Stent-related pain and urinary symptoms could be related to distal ureteral spasms or local trigone sensitivity. The possible mechanisms of benefit could be ureteral smooth muscle relaxation, affecting ureteral motility. Recent studies have demonstrated that alpha-1 blockers enhance distal ureteral stone clearance in both sexes, possibly by causing ureteral dilation/relaxation[22,23]. Recently, Davenport et al. reported that tamsulosin significantly reduced ureteric pressure in a pilot study[24]. In the present study, silodosin significantly reduced the prevalence of urinary symptoms. Such results were similar to those results analyzed by Dellis and Yakoubi[25,26]. Stent-related pain was significantly less in patients receiving silodosin, who required significantly fewer analgesics, as previously reported[25,26]. Silodosin reduced not only pain during voiding, but also loin pain, possibly by reducing urine reflux by better bladder neck relaxation.

Sexual dysfunction due to a decreased libido and decreased self-confidence was demonstrated in patients with stents and was associated with the urinary symptoms and pain attributed to the presence of the double-J stent in the study by Joshi et al. [20]. The decrease in urinary symptoms and associated pain in patients with double-J stents receiving silodosin still cannot improve sexual performance status in such patients in the study; this finding is opposed to those of previous reports[25,26]. However, the general health index score was significantly better in patients receiving silodosin; thus, these patients were more active, calm, and happy with their life[25,26]. Additional problems, such as urinary tract infections, leading to the need for medical assistance or even hospitalization, were similar in both groups, probably reflecting proper stent placement and explaining in part why days off work were similar in both groups. Feelings for future stent placement were greater in the silodosin group. Stenting makes patient happy, maybe due to the improvement of urinary tract symptoms and pain. Several studies have demonstrated the beneficial effects of alpha blockers in the treatment of voiding symptoms in women[27,28]. Urodynamic studies in women with frequency, ur-

gency, and urge incontinence have shown a modulating effect of alpha blockers on bladder smooth muscle[29].

We acknowledge the potential limitations of our study as reported by Deliveveliotis et al. Only a single stent, design, size, and material were evaluated; however, it has been demonstrated that the degree of stent-related symptoms is not associated with the stent characteristics (composition, style, and length), placement techniques, body height, or gender[29,30]. Moreover, the utilization of a single stent can minimize the trial variability. We performed ureteroscopic stone manipulation with routine insertion of ureteral stents for two weeks until they completed the questionnaires and terminated treatment (silodosin or placebo). Our primary objective was to evaluate whether the concept of using an alpha-1 blocker is justified. Future randomized prospective studies of a larger sample of consecutive patients with a longer follow-up might potentially overcome our limitations and compare the morbidity of stents with different characteristics and insertion indications.

CONCLUSIONS

The double-J stent has become an integral part of urologic interventions; however, stent-related morbidity is a reality in the great majority of patients. The administration of a selective alpha-1 blocker, such as silodosin, improves stent-related urinary symptoms, pain, and voiding flank pain. Future research is needed to refine the exact role and mechanisms of selective alpha-1 blockers in managing stent-related symptoms.

ACKNOWLEDGMENTS

The contributing authors declare that there is no existence of financial support in the study.

CONFLICT OF INTEREST

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

All authors have made a significant contribution to the findings and methods in the paper. All authors have read and approved the final draft. The work has not already been published and has not been submitted simultaneously to any other journal.

ABBREVIATIONS

BPH: benign prostate hyperplasia
USSQ: ureteral stent symptom questionnaire) and
IPSS: International Prostate Symptom Scale (IPSS)

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