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The effects of silodosin therapy on the parameters and patterns of ureteric jets in patients with lower urinary tract symptoms

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Abstract. – OBJECTIVE: To our knowledge, there is no study in the literature so far to investigate the effect of silodosin therapy on the ureteric jet parameters. Therefore, the objective of this study was to investigate the effect of silodosin 8 mg/day for medical therapy of lower urinary tract symptoms (LUTS) on the color flow Doppler parameters and patterns of the ureteric jets.

PATIENTS AND METHODS: This prospective cohort study included 34 male patients who presented to our outpatient clinic with the complaint of lower urinary tract symptoms (LUTS) and received silodosin 8 mg once a day as medical therapy. In the color flow Doppler examinations, ureteric jets were observed and mean flow rate (JETave), maximum flow rate (JETmax), flow duration (JETdura), and flow frequency (JETfre) were examined. In addition, patterns of the ureteric jets (JETpat) were also evaluated.

RESULTS: There was no statistically significant difference in JETave; however, JETmax, JETdura and JETfre were significantly higher at post-silodosin treatment. The patterns of ureteric jet were significantly changed following a 6-week treatment with silodosin ($p<0.001$). One ureter in the monophasic pattern group (9.1%) and three in the biphasic group (13.6%) turned to polyphasic pattern after silodosin use. None of the patients developed side effects that would require discontinuation of the drug.

CONCLUSIONS: Six-week silodosin 8 mg/day therapy for the treatment of LUTS in men changed the parameters and patterns of ureteric jets at follow-up examination. Furthermore, comprehensive studies are needed on this issue.

Key Words:
Lower urinary tract symptoms, Silodosin, Flow patterns, Ureteric jet, Color flow Doppler, Ultrasonography.

Introduction

The lower urinary tract (LUT) is responsible for efficient low-pressure urine storage with normal sensation, and periodic, complete voluntary emptying[1]. The LUT system involves the bladder, bladder outlet, urethra, and pelvic floor. Lower urinary tract symptoms (LUTS) are simply defined as urinary symptoms shared by disorders affecting the bladder and prostate in men. LUTS may include a slow or weak urine stream, hesitancy in releasing urine, difficulty in emptying the bladder, and needing to get up at night to urinate. LUTS are generally classified according to their two main functions including urine storage and voiding. The main storage LUTS include increased daytime urinary frequency, urgency, incontinence and nocturia. The main voiding symptoms are straining, slow stream, hesitancy, intermittency and terminal dribbling[2]. Urinary urgency and frequency are associated with increased use of muscarinic receptor antagonists (MRA) in men with BPE in everyday clinical practice[3]

LUTS are often seen in middle-aged and elderly men and are mostly resulted from an enlarged prostate known as benign prostate hyperplasia (BPH)[4]. Numerous evidence suggests that in addition to ageing, modifiable factors such as increasing prostate volume, hormonal imbalance, obesity, diet, dyslipidemia, metabolic syndrome, hypertension, smoking and alcohol, also contribute to the development of LUTS[5]. LUTS are estimated to affect approximately 2.3 billion people that corresponds to 45.8% of the world population in 2018[6]. LUTS are caused by multiple pathological factors, including abnormal function in prostate, bladder, and urethra, inflammation,

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metabolic syndrome and neurological diseases[7]. Estimated global prevalence of LUTS about 50%[8]. It is estimated that there would be 42 million men in the USA with LUTS by 2025, suggesting an increasing burden of LUTS.

The ureteric jet is a phenomenon resulting from urine ejection into the vesicle lumen by ureteral peristalsis[9]. This phenomenon can be defined as the visualization of the normal physiological efflux of urine from the distal end of both ureters into the bladder. The diagnosis of urinary diseases is highly associated with the patterns of the ureteric jet, including monophasic, biphasic, triphasic, polyphasic, square and continuous patterns[10]. A monophasic jet is characterized by one peak. Biphasic and triphasic jets are characterized by two and three peaks, respectively. Four or more peaks characterize a polyphasic jet[11].

LUTS are treated with medication, surgery, minimal invasive procedures, and neuromodulation therapy[12]. Medical therapy for LUTS includes α-adrenergic-receptor blockers, 5α-reductase inhibitors, antimuscarinic therapy and phosphodiesterase-5 inhibitor therapy[13]. Among the medical treatment options, alpha-blockers, which provide relaxation in the bladder neck and enlargement of the prostatic urethra, are frequently used. Alpha-blockers exert their effect by the inhibition of alpha-adrenergic receptors found on smooth muscle in the prostate and bladder neck. Silodosin is a selective alpha-1a adrenergic antagonist (Alpha blocker) used in the treatment of BPH. Its effect on alpha-1b adrenergic receptors presents in arterioles, that are responsible for the antihypertensive effects of the nonspecific alpha-1 adrenergic blockers, is minimal[14]. Silodosin has high affinity for the alpha-1 adrenergic receptors in the prostate, bladder and prostatic urethra and relaxes the smooth muscle, facilitating urinary flow and relieving LUTS symptoms. In an explorative study, the effect of silodosin 8 mg/day on obstruction urodynamic parameters was investigated in 30 patients. At the end of the study, all enrolled patients reported that their condition improved enough to delay or spare surgery[15]. To our knowledge, there is no study in the literature so far to investigate the effect of silodosin therapy on the ureteric jet parameters. Therefore, the objective of this study was to investigate the effect of silodosin 8 mg/day for medical therapy of LUTS on the color flow Doppler parameters and patterns of the ureteric jets.

Patients and Methods

Study Sample

Before the beginning of the study, a power analysis was performed in order to determine the number of patients that should be enrolled. The study of a continuous response variable from matched pairs of the subjects was planned. Previous data indicated that the difference between the responses of the matched pair was normally distributed with standard deviation of 3.9[16]. It was calculated that when the true difference between the responses of matched pairs is 1.5, the number of subjects required for being able to reject the null hypothesis with zero response difference and a power of 90% was found as 60. The type I error probability associated with the test of the null hypothesis was 0.1.

This prospective cohort study included male patients who presented to our outpatient clinic with the complaint of lower urinary tract symptoms (LUTS) and received silodosin 8 mg once a day as medical therapy between June 2019 and December 2019.

Study Procedure

A total of 34 patients who presented with the symptoms of LUTS and were treated with silodosin 8 mg/day (Urorec, Recordati, Milano, Italy) were included in the study. Patients with a history of previous ureter, bladder and prostate surgery, those using other drugs, patients with bladder or ureteral stones, obese patients, those with a prostate volume > 40 cc or marked protrusion to the bladder, patients who didn't have at least 250-mL urine storage capacity, those for whom a surgical decision was made at the first admission, patients with known allergy or sensitivity to silodosin, and patients aged under 40 years and above 75 years were excluded from the study.

Patients' age and body mass index values were recorded. The patients were told to use silodosin 8 mg oral tablets once a day for six weeks and then to re-visit for follow-up. In the follow-up, after the patients were checked for LUTS, color flow Doppler (CFD) was performed to examine the changes in the ureteric jets. The patients were told to drink 1,000 ml of water within one hour before the procedure, which was performed when there was 250-400 ml of urine in the bladder. In the color flow Doppler examinations, ureteric jets were observed and mean flow rate (JETave), maximum flow rate (JETmax), flow duration (JETdura), and flow frequency (JETfre) were examined. In addition, patterns of the ureteric jets (JETpat) were also noted as described by Leung et al[10].

Ethical Considerations

The study protocol was approved by the Istanbul Health Sciences University, Prof Dr İlhan Varank Training and Research Hospital, Scientific Research Ethic Committee dated 19/08/2020 and numbered 2020/15. All patients included in the study were informed in detail about the objectives of the study and gave written informed consent. This study was executed in line with the relevant ethical principles of the Declaration of Helsinki (DoH) revised in 2013.

Statistical Analysis

The study data were subjected to the statistical analysis with the SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) statistical software. Normal distribution of the variables was evaluated with the Shapiro-Wilks test. Since the variables were non-normally distributed, Wilcoxon and Chi-square tests among the non-parametric tests were used for the comparison of pre- and post-treatment data. $p<0.05$ values were considered statistically significant.

Results

A total of 34 patients, aged between 40 and 75 years and 68 ureters were included in the study. All patients were included in the final analysis, because no patient was lost from the follow-up or discontinued taking the drug due to side effects. The mean age of the patients was 56.9±6.15 years. The mean body mass index was calculated as 28.6±3.3 kg/m^2.

When pre- and post-treatment ureteric jet parameters were compared, no statistically significant difference was found in JETave. However, JETmax, JETdura and JETfre were significantly higher at post-silodosin treatment. The comparison of the ureteric jet parameters before and after silodosin therapy is given in Table I.

The patterns of ureteric jet were significantly changed following 6-week treatment with silodosin ($p<0.001$). One ureter in the monophasic pattern group (9.1%) and three in the biphasic group (13.6%) turned to polyphasic pattern after silodosin use. Post-silodosin changes in the ureteric jet patterns are presented in Table II. Percentage distribution of the ureteric pattern pre- and post-silodosin treatment is shown in Figure 1.

None of the patients developed side effects that would require discontinuation of the drug. Twenty-one (61.8%) patients complained of anejaculation. This situation was explained by talking to the patients and it was ensured that they continued to use the drug.

Discussion

In the present study, we investigated the effects of 6-week silodosin therapy administered in 34 patients with LUTS on the CFD parameters and patterns of the ureteric jet. LUTS are common in men with up to 41% of men aged over 40 years reporting these symptoms[17]. In addition, BPH can significantly contribute to the onset of LUTS in a portion of men aged over 40 years[18]. In our study, patients aged between 40 and 75 years with a mean age of 56.9±6.15 years. Kawahara et

Table I. Comparison of the pre- and post-treatment ureteric jet parameters.

	Pre-silodosin	Post-silodosin	*p*-value
Jetave	21.21±7.56	22.1±6.76	0.095
Jetmax	82.88±33.42	92.31±37.67	**0.012**
Jetdura	5.48±2.61	5.88±3.15	**<0.001**
Jetfre	3.63±1.38	3.81±1.26	**<0.001**

Table II. Comparison of the pre- and post-treatment ureteric jet patterns.

		After					
		Monophasic	Biphasic	Triphasic	Polyphasic	Total	*p*-value
Before	Monophasic	6	3	2	0	11	**<0.001**
	Biphasic	2	12	5	3	22	
	Triphasic	1	3	10	4	18	
	Polyphasic	1	1	1	14	17	
	Total	10	19	18	21	68	

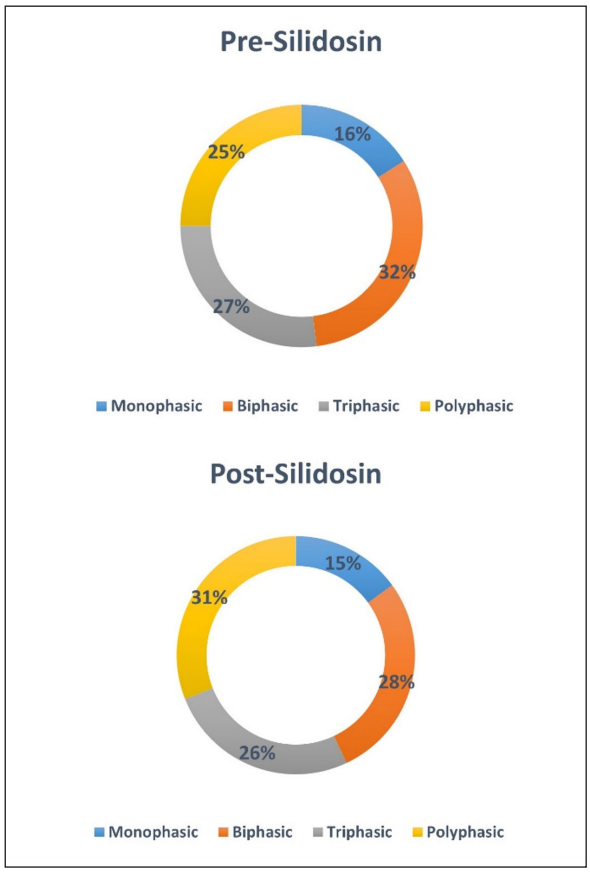

Figure 1. Changes in the ureteric jet patterns following silodosin therapy.

al[19] investigated the effects of smoking on LUTS and the patients included in that study aged between 40 and 70 years. Sunter et al[20] reported the mean age of the patients with LUTS as 53.8 ± 10.0 years. The range of the mean age is similar between the studies and indicates an increased risk of developing LUTS in men aged over 40 years.

In the literature, ureteric jet parameters, including JETave, JETmax, JETdura and JETfre have been used to evaluate response to therapeutic methods[21,22]. Ureteric jets have been analyzed in various patient groups such as urinary obstruction, ureteral injury, vesicoureteral reflux, and significant findings have been reported[23,24]. The ureteric jet frequency could be an important index for the diagnosis of obstructive uropathy[25]. A frequency of less than two per minute may indicate partial obstruction[26]. Although many studies[10,27] have been published about the ureteric jet patterns and parameters demonstrated by color flow Doppler ultrasonography, in the literature searching we could not find a study investigating the effect of silodosin, a selective alpha-1a adrenergic antagonist, on ureteric jets.

Among the ureteric jet parameters, JETave and JETmax have been reported between 16-150 in the literature[27]. Consistently with the literature, in our study, the mean JETave and JETmax values were 21.21±7.56 and 82.88±33.41 in the first measurement and 22.1±6.76 and 92.31±37.67 in the second measurement. However, in the present study, no statistically significant difference was found in JETave at 6-week follow-up compared to the baseline values with silodosin therapy (p=0.095). In a study by Celik et al[16] with kidney transplantation patients, ureteric jet patterns significantly changed 12 months after removal of Double J Stent (DJS) compared to 6 months after the removal (p=0.035).

There are six different ureteric jet patterns identified under different pathological conditions. Among these patterns, biphasic, triphasic and polyphasic patterns indicate a mature complex jet, while monophasic pattern shows an immature jet, especially in young patients[9]. In our study, the predominant pattern was biphasic. Yildirim et al[28] found the predominant pattern as monophasic in their patients with non-obstructive nephrolithiasis. In another study by Lins et al[11], the most common ureteric jet pattern was square in asymptomatic children. We attributed the difference results between the studies to the examined urologic pathology and patient groups included.

In our study, there was a statistically significant difference in the patterns of ureteric jets between pre- and post-silodosin therapy. The ureteric jet pattern was monophasic in 16%, biphasic in 32%, triphasic in 27% and polyphasic in 25% of the 68 ureters before silodosin therapy. These patterns changed to 15% monophasic, 28% biphasic, 26% triphasic and 31% polyphasic six weeks after the beginning of silodosin therapy. There was an overall statistical difference between the pre- and post-treatment values (p<0.001). In a study by Masciovecchio et al[29] silodosin therapy improved IPSS symptoms score and QoL in patients with LUTS associated with BPE who were not-responders to tamsulosin therapy. On the other hand, in the literature search, we could not find any similar study to compare our results, indicating the need for further studies on this issue.

Study Limitations

The main limitation of this study is the relatively small number of patients. In addition, a control group of healthy individuals could be created. Our findings showed difference in 6-week follow-up and longer-term measurements could be made to see if a difference develops in ureteric parameters and patterns. Nevertheless, there is no study in the literature to investigate the effect of alpha-1 adren-

ergic antagonists used for the treatment of LUTS on ureteric parameters and patterns.

Conclusions

Six-week silodosin 8 mg/day therapy for the treatment of LUTS in men changed the parameters and patterns of ureteric jets at follow-up examination. There was no study to compare our results in the literature. Furthermore, comprehensive studies are needed on this issue.

Acknowledgements
Not applicable.

Conflict of Interest
Authors did not report any conflict of interest.

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The study did not receive financial support.

Data Availability
Data used in this study are included in the manuscript.

Ethics Approval
The study protocol was approved by the Istanbul Health Sciences University, Prof Dr İlhan Varank Training and Research Hospital, Scientific Research Ethic Committee with the 19/08/2020 dated and 2020/15 numbered decision.

Informed Consent
All patients included in the study were informed in detail about the objectives of the study and gave written informed consent.

Authors' Contribution
Conception and design: MYS, KMA
Analysis and interpretation: MYS, TYK
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Writing the article: MYS, GB
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