KJU
Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2013.54.10.697

Sexual Dysfunction/Male Infertility

Effects of Low-Dose Tamsulosin on Sexual Function in Patients With Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia

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Purpose: The aim of the present study was to evaluate the effects of low-dose tamsulosin on sexual function in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia.

Materials and Methods: A total of 138 male LUTS patients aged more than 50 years with an International Prostate Symptom Score (IPSS) ≥8 were enrolled in this open-label, multicenter, prospective, noncomparative observational study. Clinical assessments included IPSS, quality of life (QoL) index, International Index of Erectile Function (IIEF), Danish Prostate Symptom Score (DAN-PSS), and an early morning erection questionnaire. The data were recorded at baseline and at 1 and 3 months after treatment with tamsulosin 0.2 mg/d. Adverse events were analyzed in all patients.

Results: During the study period of 3 months, the IPSS and QoL index significantly improved from baseline by −11.40±9.40 and −1.11±1.36, respectively ($p<0.001$). However, there were no clinically relevant changes in total IIEF score (mean difference, 1.63±15.50; p=0.406) or the 5 subdomains ($p>0.05$). Furthermore, DAN-PSS weighted scores (A×B) showed no clinically relevant changes (mean difference on Q1, Q2, and Q3: −0.45±2.94, 0.27±2.50, and −1.27±2.27, $p>0.05$). In addition, there were no clinically significant changes in responses on the early morning erection questionnaire.

Conclusions: Tamsulosin at the dose of 0.2 mg significantly improved the IPSS and the QoL index compared with baseline. However, tamsulosin did not exhibit any significant impact on sexual function or any negative impact on ejaculatory function.

Keywords: *Ejaculation; Erectile dysfunction; Lower urinary tract symptoms; Prostatic hyperplasia; Tamsulosin*

Article History:
received 29 May, 2013
accepted 2 July, 2013

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INTRODUCTION

Lower urinary tract symptoms (LUTS) are the most common complaint in aging urologic patients. The prevalence of histological benign prostatic hyperplasia (BPH) is between 8% and 90% depending on the age of the patient [1]. The Massachusetts Male Aging Study reported that about 35% of aging men have moderate to severe erectile dysfunction (ED) and that older people indeed have an interest in sex and active sexual relationships [2-4]. However, it has been assumed that sexual dysfunction and LUTS are natural consequences of the human aging process and that no relationship exists between them. In fact, most guidelines for ED evaluation and treatment have disregarded LUTS until now.

The Multinational Survey of the Aging Male (MSAM-7) suggested that the relationship between ED and LUTS is independent of age or underlying comorbidities [4]. In

agreement with this observation, other studies also reported that LUTS were an independent prognostic factor for ED [5-8]. Although definite pathophysiological mechanisms have not yet been revealed to correlate the relationship between ED and LUTS, several mechanisms including the alteration of α-adrenergic receptor subtypes and an increase in α-adrenergic activity have been proposed from the literature [9]. An imbalance in α-adrenergic receptors in LUTS patients increases the smooth muscle tone of the bladder neck and prostate capsule [10]. Corpus cavernosum smooth muscle relaxation is a major component of penile erection, and the abnormal activation of α-adrenergic receptors through the sympathetic system causes early penile detumescence [11]. Thus, decreased smooth muscle tone through the alteration of α-adrenergic receptors may improve LUTS and ED at the same time.

Tamsulosin is a prostate-selective α1-adrenergic receptor antagonist. In a meta-analysis of two randomized, placebo-controlled studies in symptomatic BPH patients, tamsulosin 0.4 mg once daily was found to be safe and well-tolerated and improved the urinary flow rate as well as Boyarsky symptom scores [12]. In a meta-analysis conducted by the American Urological Association, tamsulosin exhibited similar decreases in libido and erectile function compared with a placebo group. However, tamsulosin was associated with a higher incidence of dose-dependent (0.4 mg vs. 0.8 mg) ejaculatory dysfunction [13]. The aim of the present study was to evaluate the effects of tamsulosin 0.2 mg on sexual function in patients with LUTS suggestive of BPH.

MATERIALS AND METHODS

Between October 2009 and October 2010, a total of 138 male LUTS patients aged 50 years and older with an International Prostate Symptom Score (IPSS) ≥8 were enrolled from 3 centers for this open-label, multicenter, prospective, noncomparative observational study. Because a minimal treatment effect of tamsulosin was defined as 25% improvement at baseline with a 0.5% significance level, 90% power, and 10% dropout rate, 150 patients were required. All patients consented before being enrolled in this study. The Institutional Review Board of 09-86 approved the prospective analysis of this patient population.

The exclusion criteria were residual urine volume of more than 100 mL; presenting urinary tract infection or urinary calculi; history of prostate surgery, pelvic surgery, or urinary retention; interstitial cystitis; bladder cancer; neurogenic bladder; elevated prostate specific antigen (PSA≥4 ng/mL); presenting renal disease or liver disease; uncontrolled diabetes mellitus; hematuria of an unknown cause; androgen hormone treatment; treatment with other α-blocker medication within 1 week or treatment with 5-alpha reductase inhibitor; treatment with anticholinergics, diuretics, selective–serotonin reuptake inhibitors, or tricyclic antidepressant medication within 4 weeks; and ED treatment.

Baseline assessments included medical history, physical examination, body mass index (BMI), blood pressure, IPSS, quality of life (QoL) index, Danish Prostate Symptom Score (DAN-PSS), International Index of Erectile Function (IIEF), an early morning erection questionnaire, maximum flow rate (Qmax), postvoided residual urine volume (PVR), transrectal ultrasound, and PSA [14-16]. Data for the IPSS, DAN-PSS, and IIEF were recorded at 1 and 3 months after treatment. Drug compliance and adverse events were also analyzed in all patients.

A total of 138 patients were divided into two groups according to IPSS: patients with moderate symptoms (8≤IPSS≤19) and patients with severe symptoms (20≤IPSS). For the analysis of clinicopathologic variables between the two groups, Student t-test was used. Repeated-measures analysis of variance was carried out to compare the outcomes of each group. All statistical analysis was performed by use of IBM SPSS ver. 19.0 (IBM Co., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

One hundred thirty-eight patients were registered for this study. Forty patients dropped out at the 1-month follow-up and 31 patients dropped out at the 3-month follow-up. Sixty-seven patients (48.5%) completed the study at 3 months after treatment.

The baseline analysis of clinicopathologic data showed the patients' mean age to be 61.3±6.9 years. Mean prostate volume and PSA were 30.4±13.7 mL and 1.36±1.56 ng/dL, respectively. The mean IPSS was 17.0±6.7 and the mean IIEF score was 32.7±19.9. Ninety patients were in the moderate symptom group and 48 patients were in the severe symptom group. Age, BMI, prostate volume, PSA, PVR, and systolic/diastolic pressure were not significantly different between the groups. A lower Qmax was observed in the severe symptom group with marginal significance (p=0.065). The overall score and scores for each domain of the IIEF were not significantly different on the basis of the IPSS. However, the overall satisfaction score was lower in the severe symptom group with marginal significance (p=0.084). Descriptive analysis of the DAN-PSS indicated that the severe symptom group had higher ED, a decreased amount of semen, and decreased ejaculatory dysfunction (p=0.038, p=0.001, and p=0.072) (Table 1).

During the study period, IPSS and QoL index were significantly improved from baseline by −11.4±9.40 and −1.11±1.36, respectively (both $p<0.001$) (Fig. 1). However, there were no clinically relevant changes in total IIEF score (mean difference, 1.63±15.50; p=0.406) or in any of the five domains (all $p>0.05$) (Fig. 2). Also, none of the DAN-PSS weighted scores (A×B) showed clinically significant changes (all $p>0.005$) (Fig. 3). In addition, there was no clinically significant change in scores on an early morning erection questionnaire (mean difference, 0.26±1.08; p=0.062). Moreover, these results were not significantly different according to IPSS symptom score.

TABLE 1. Demographics and other baseline characteristics

Variable	Total	8≤IPSS≤19	IPSS≥20	p-value
Patients	138	90	48	
Age (y)	61.3±6.9	61.3±7.0	61.4±7.0	0.998
BMI (kg/m^2)	24.6±2.6	24.7±2.7	24.3±2.4	0.488
Prostate volume (mL)	30.4±13.7	30.1±15.0	30.9±11.1	0.754
PSA (ng/dL)	1.36±1.56	1.4±1.8	1.2±0.9	0.697
Maximum flow rate (mL/s)	12.9±6.6	13.7±7.1	11.4±5.3	0.065
Post-voided residual urine	37.0±51.9	34.7±50.1	41.5±55.5	0.317
Blood pressure (mmHg)				
Systolic pressure	130.7±15.7	130.0±16.0	131.9±15.3	0.498
Diastolic pressure	81.7±11.1	81.3±11.3	82.6±10.6	0.506
IPSS				
Overall score	17.0±6.7	13.0±3.6	24.5±4.0	<0.001
Storage symptom score	6.6±3.2	5.1±2.2	9.4±2.8	<0.001
Voiding symptom score	10.4±4.7	7.9±3.3	15.1±3.1	<0.001
QoL score	3.9±1.3	3.6±1.3	4.6±1.2	<0.001
IIEF				
Overall score	32.7±19.9	34.4±19.3	29.6±20.9	0.177
Erectile function	13.7±9.7	14.3±9.4	12.4±10.1	0.280
Orgasmic function	5.0±3.5	5.3±3.3	4.4±3.8	0.169
Sexual desire	4.1±2.2	4.3±2.2	3.8±2.3	0.164
Intercourse satisfaction	5.0±3.6	5.2±3.5	4.4±3.6	0.208
Overall satisfaction	5.0±2.3	5.2±2.1	4.5±2.5	0.084
DAN-PSS				
Weighted 1A×1B	2.1±2.6	1.8±2.4	2.8±2.9	0.038
Weighted 2A×2B	1.8±2.3	1.4±2.2	2.7±2.4	0.001
Weighted 3A×3B	0.6±1.7	0.6±1.8	0.8±1.5	0.072
Early morning erection index	2.4±1.1	2.4±1.0	2.4±1.3	0.978

Values are presented as mean±standard deviation.
BMI, body mass index; PSA, prostate-specific antigen; IPSS, International Prostate Symptom Score; QoL, quality of life; IIEF, International Index of Erectile Function; DAN-PSS, Danish Prostate Symptom Score.

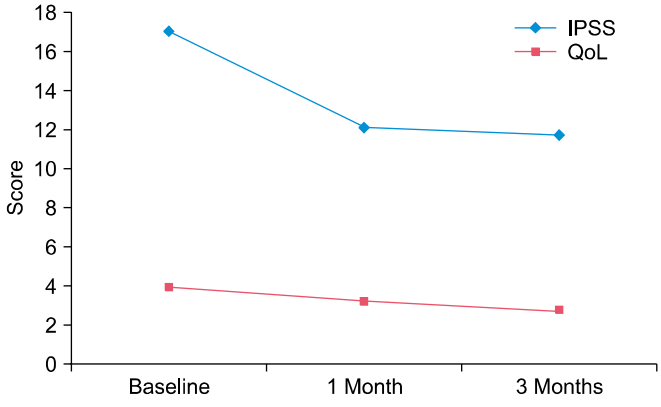

FIG. 1. International Prostate Symptom Score (IPSS). IPSS and quality of life (QoL) score decreased during the study periods.

In this study, tamsulosin 0.2 mg showed an incidence of de novo ejaculatory discomfort of 10.2% at 1 month and 6.0% at 3 months. Adverse events were reported for four cases during the entire study period: two cases of headache and one each of dizziness and dyspepsia. However, no serious adverse events were observed. One patient with adverse events dropped out of the study and all other patients continued the study.

DISCUSSION

Although α-adrenergic blockers were initially developed for the treatment of hypertension, with the advent of more specific and effective treatments, they are no longer considered the first-line treatment [17]. However, α-blockers are widely used for the treatment of LUTS suggestive of BPH. Tamsulosin is a uroselective α-blocker and does not affect blood pressure. Tamsulosin was found to be safe and effective in patients with LUTS/BPH and does not result in clinically significant changes in blood pressure as reported by Chapple et al. [12].

Alpha-blockers show no difference in their efficacy for treatment of LUTS despite their varied affinity for α-receptor subtypes [18]. However, the side effect profiles differ owing to the presence of differential α-receptors in the peripheral vessels, which causes differential vasodilatory effects, such as orthostatic hypotension, syncope, headache, and dizziness. Nonselective α-receptor blockers, such as doxazosin and terazosin, are more frequently associated with the above events than are selective α-receptor blockers, including tamsulosin. In a similar manner, α-blockers

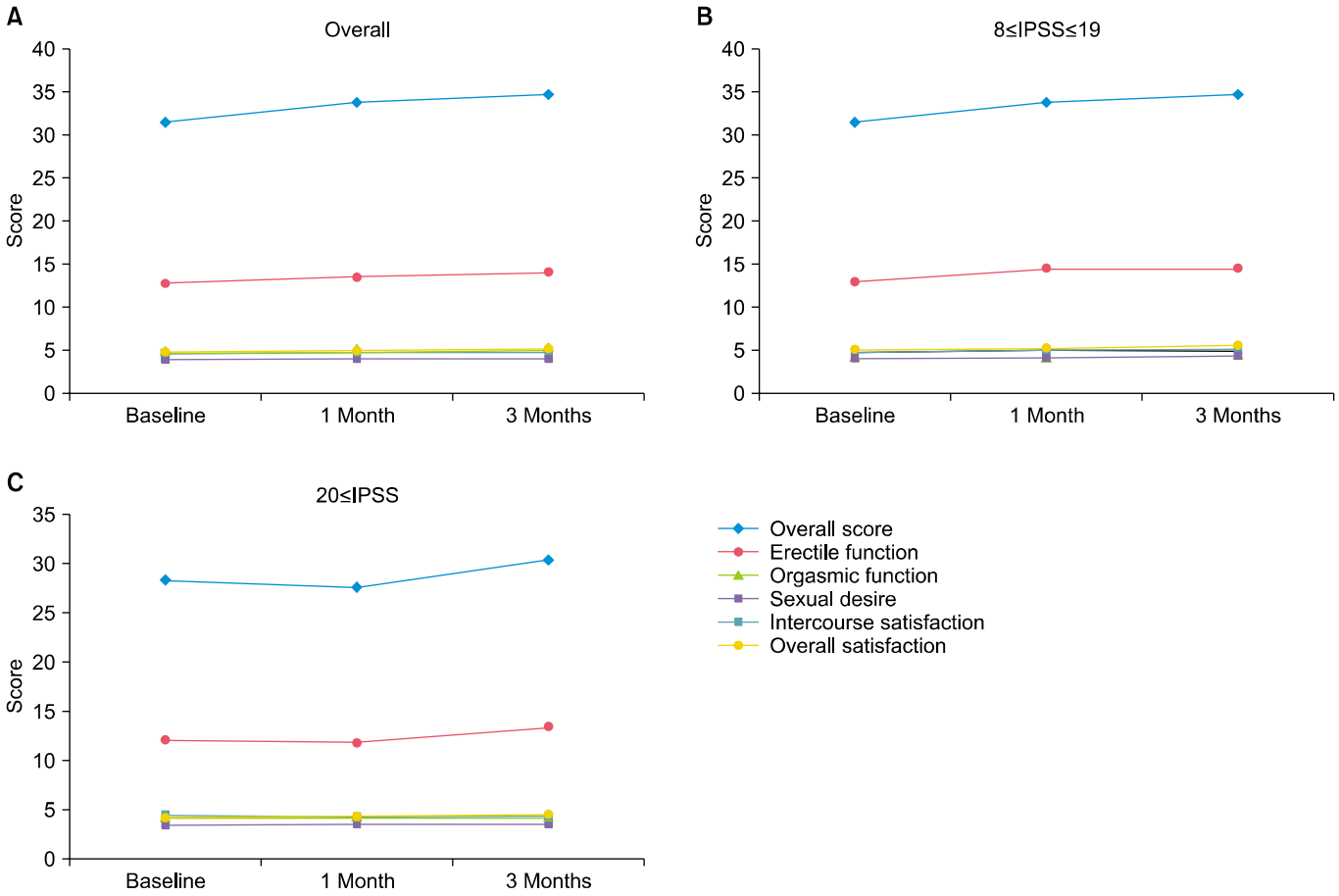

FIG. 2. International Index of Erectile Function (IIEF) score. (A) There were no clinically relevant changes in total IIEF score or in any of the five domains. (B, C) These results did not differ according to International Prostate Symptom Score (IPSS).

also exhibit a differential adverse effect on sexual function [19]. Recent studies on sexual dysfunction have reported that tamsulosin shows effects on decreased libido and ED similar to those of placebo. However, tamsulosin exhibited a significantly higher incidence of ejaculatory dysfunction than seen with placebo or other α-receptor blockers [13]. In a placebo-controlled study, the incidence of dysfunctional ejaculation with tamsulosin was found to be increased dose-dependently: 6% and 18% at the doses of 0.4 mg and 0.8 mg, respectively [20]. A phase III clinical study reported that tamsulosin exhibited a dose-dependent higher incidence of dysfunctional ejaculation, 10% to 26% at 53 weeks and 30% at 65 weeks [21,22].

It is noteworthy to mention that in the studies discussed above, a relatively high dose (0.4 mg or 0.8 mg) of tamsulosin was used, higher than the regular dose (0.2 mg) in Korea. In fact, there are few reports on the effects of tamsulosin 0.2 mg on sexual dysfunction. As reported by Yokoyama et al. [23], tamsulosin 0.2 mg showed an incidence of *de novo* ejaculatory discomfort of 8.3% (only 1 of 12 patients). These data are similar to the present study (10.2% at 1 month, 6.0% at 3 months). However, the study used an invalidated questionnaire and the number of patients was also very small. In the present study, we used the DAN-PSS, a well-validated questionnaire for the evaluation of ejaculatory dysfunction [16]. In patients who received tamsulosin 0.2 mg, DAN-PSS weighted scores showed no clinically relevant changes ($p > 0.05$), which suggests that tamsulosin 0.2 mg did not have a significant negative impact on ejaculatory function.

Three subtypes of α1-receptors are found in the human penis (alpha 1d, alpha 1b, and alpha 1a) and the alteration of α-adrenergic receptor subtypes may be related to LUTS and ED [9,24]. In contrast with the utility of phenylephrine, a selective α1-adrenergic receptor agonist, in the treatment of priapism, it is reasonable to speculate that α-blockers may have erectile effects in the penis. In contrast, previous clinical studies with α-blockers reported more adverse effects than beneficial on erectile function, which could be a result of the blood pressure–lowering effect or another unknown mechanism mediated by α-blockers. In another report, treatment with tamsulosin 0.4 mg was associated with a high incidence of impotence [25]. However, this was refuted by Hofner et al. [26] and Buzelin et al. [27], who reported that tamsulosin at the dose of 0.4 mg is tolerable and does not have a negative effect on erectile function. In the present study, the total IIEF score and the scores on the 5 subdomains did not change significantly from base-

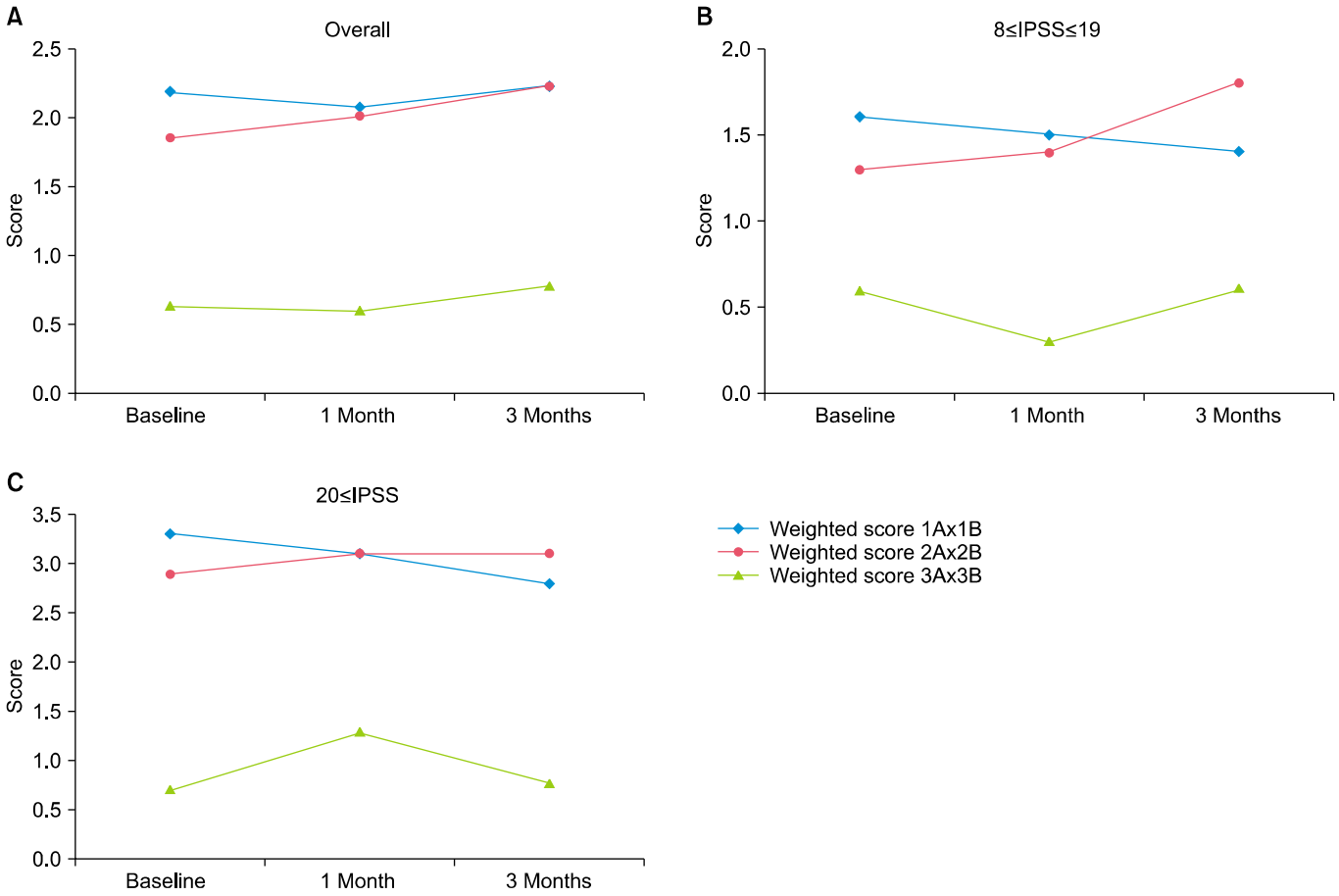

FIG. 3. Danish Prostate Symptom Score (DAN-PSS). (A) DAN-PSS weighted scores (A×B) showed no clinically relevant changes. (B, C) These results did not differ according to International Prostate Symptom Score (IPSS).

line at 1 or 3 months. The scores on the early morning erection questionnaire also did not show any significant changes, which suggests that tamsulosin 0.2 mg did not exhibit any significant impact on sexual function.

Because tamsulosin is prostate selective, it shows fewer adverse effects in the treatments of LUTS. Therefore, tamsulosin is the most widely prescribed medication among other α-blockers. Previous studies reported that tamsulosin is an effective medication at doses of 0.2 to 0.8 mg [20,28]. In contrast to the dosing pattern of tamsulosin 0.4 mg and 0.8 mg in the United States and Europe, Korea and other East Asian countries widely use tamsulosin 0.2 mg owing to the smaller body surface area of Asian men compared with Western men. A study on the initial low-dose medication showed that tamsulosin 0.2 mg is effective in Korean men [29]. Our data also indicated that the IPSS decreased markedly at 1 month (17.02±6.66 vs. 12.08±7.09, $p<0.001$) and a sustained treatment effect was observed at 1 and 3 months (12.08±7.09 vs. 11.73±7.49, p=0.764). In addition, the QoL score decreased steadily with treatment duration (3.90±1.18 vs. 3.17±1.39, $p<0.001$, and 3.17±1.39 vs. 2.78±1.44, p=0.088). In agreement with previous studies, these results suggest that an initial dose of tamsulosin of 0.2 mg is effective for treatment in LUTS patients.

IIEF scores did not differ significantly according to the IPSS with the exception of overall satisfaction (p=0.084). However, DAN-PSS weighted scores showed significant differences. Patients with severe LUTS compared with moderate LUTS suffered from ejaculatory dysfunction. However, although the total IPSS improved with tamsulosin medication, the DAN-PSS and IIEF did not show meaningful changes in men with either moderate or severe LUTS. Further studies are needed to fully understand this phenomenon.

A limitation of the present study was the relatively large number patients who dropped out of the study and the difference in the rate of loss to follow-up among the centers. Hence, there may have been a selection bias even though this was a prospective study. However, data from patients who completed the study were collected, and the demographic data from this study agreed with those of previous studies. Another limitation was the measurement of ejaculatory dysfunction, because objective measures such as semen volume, sperm concentration, and urine analysis after ejaculation were not included at this study. However, we made an effort to quantify the ejaculatory dysfunction by using a well-validated questionnaire such as the DAN-PSS.

CONCLUSIONS

Tamsulosin at the dose of 0.2 mg improved the IPSS and QoL index significantly from baseline. However, it did not have any significant impact on sexual function or any negative impact on ejaculatory function.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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