Voiding Dysfunction/Female Urology

Effect of Patient-Optimized Doses of Tamsulosin on Erectile Function in Men With Erectile Dysfunction and Lower Urinary Tract Symptoms

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Purpose: To investigate the relationship of improvement in erectile function (EF) with improvement in lower urinary tract symptoms (LUTS) and to assess the contribution of tamsulosin dose to the improvement of EF apart from the indirect influence of LUTS improvement in men with LUTS and erectile dysfunction (ED).

Materials and Methods: Fifty patients received tamsulosin 0.2 mg/d for the first 4 weeks and were subsequently divided into two groups by patient-reported outcomes. Nonescalators were maintained starting dose and escalators increased to 0.4 mg for the remaining 8 weeks. International Prostatic Symptom Score (IPSS) and International Index of Erectile Function (IIEF-5), and underwent uroflowmetry were evaluated at baseline, and weeks 4 and 12.

Results: LUTS parameters were significantly improved in both groups but insignificant between the 2 groups. The degree of the improvement in the total IPSS and in the voiding, storage, and quality of life (QoL) subscores were significantly correlated with the degree of the improvement in EF; this was especially prominent in patients successfully treated LUTS. The escalators experienced a significantly greater increase in IIEF-5 scores than did the nonescalators (3.3 vs. 1.5).

Conclusions: Dose escalation provided similar LUTS improvement in patients with refractory to starting dose. The improvements of LUTS were correlated with the improvement of EF. The increase in the IIEF-5 score was significantly higher in escalators. These findings imply that tamsulosin may contribute to the improvement in EF through the improvement of LUTS and QoL and direct relaxation of the corpus cavernosum in a dose-dependent fashion.

Keywords: *Erectile dysfunction; Prostatic hyperplasia; Tamsulosin*

INTRODUCTION

Erectile dysfunction (ED) and lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH) increase concomitantly with increasing age, negatively affect quality of life (QoL), and have a common pathophysiology [1,2]. Over the years, four possible pathophysiological mechanisms have been proposed to explain the link between the two diseases. These include the following components: alteration in nitric oxide bioavailability, α1-adrenergic receptor (AR) hyperactivity, pelvic atherosclerosis, and sex hormones [3,4].

Since the predominance of mRNA of the α1A- and α1D-AR subtypes was revealed in human corpus cavernosum, multiple reports have shown that the selective α1-AR antagonists for LUTS positively affect erectile function (EF), although some reported that this was linked with a decrease of libido and ejaculatory dysfunction [5-10].

Meanwhile, prospective multicenter studies and randomized controlled trials showed that there was an addictive effect on EF of the combination of a phosphodiesterase-5 inhibitor (PDE5I) and an α1-AR antagonist but no improvement in EF with an α1-AR antagonist alone, particularly tamsulosin [11-14]. Thus, the effect of a single α1-AR antagonist on EF remains debatable. Current clinical results indicate that α1-AR antagonists may contribute to improvement in EF through alterations in penile sympathetic activity with the improvement of LUTS, although EF may be improved either indirectly through an improvement of LUTS or directly through effects on the corpus cavernosum [15].

In this trial, we aimed to investigate the relationship between improvement in EF and improvement in LUTS and to assess the contribution of dose to the improvement in EF apart from the indirect influence of LUTS improvement. The study population was stratified into dose nonescalators and escalators according to the efficacy and tolerability of 0.2 mg/d tamsulosin for 4 weeks.

MATERIALS AND METHODS

The design of this study was a 12 week, single-center, open-label, flexible-dose prospective trial. Fifty patients with concurrent LUTS/BPH and ED were evaluated over a period of 6 months from July 2009 to February 2010. The inclusion criteria were as follows: age 45 to 65 years with active sexual behavior, a total International Prostate Symptom Score (IPSS) of $\geq$8, and an International Index of Erectile Function (IIEF-5) score of 10 to 20. We excluded patients with the following: prostate cancer, with or without medical or surgical treatment; administration of 5α-reductase inhibitors or sex hormone agents; severely impaired BPH requiring surgical treatment; other urological diseases affecting urinary tract symptoms; and life-threatening conditions. We also excluded patients lacking a partner for sexual intercourse. All patients provided informed consent before initiating this trial, and the institutional review board of our center approved the study.

All patients underwent a routine physical examination, including measurement of blood pressure and pulse rate and a digital rectal exam. Additionally, serum prostate-specific antigen (PSA), urinalysis, transrectal ultrasound (TRUS) of the prostate, uroflowmetry (UFM), and postvoid residual urine (PVR) volume tests were performed. The IPSS and IIEF-5 questionnaires were completed and scored at the first visit to the outpatient clinic. The IPSS, IIEF-5, and UFM with PVR were repeated at weeks 4 and 12.

Fifty patients were allowed to decide at week 4 to either maintain the 0.2 mg/d tamsulosin dosage (nonescalators) or to increase their dose to 0.4 mg once daily (escalators) for the remaining 8 weeks. The patients made their decision on the basis of a discussion between the patient and a physician regarding the efficacy and tolerability of treatment according to the clinical global impression of change (CGIC). The CGIC requires the patient to complete the sentence, "Compared with before starting treatment, would you describe your problem as…," with "much worse," "worse," "slightly worse," "no change," "slightly better," "better," or "much better" as responses. When patients answered "better" or "much better," they were grouped as nonescalators; the others were chosen as escalators. The classification for the improvement of LUTS at week 12 was based on the CGIC. We also checked for adverse events, including dizziness, headache, postural hypotension, and ejaculatory problems.

The quantitative results are presented as mean±standard deviations. Statistical analyses of all efficacy variables were performed by using a two-tailed Student's t-test, and statistical significance was assessed for p-values of $<$0.05.

RESULTS

Of the 50 subjects with LUTS and ED who were analyzed in the study, the doses of 26 (52%) were escalated to 0.4 mg/d tamsulosin from the starting dose of 0.2 mg/d at week 4. Two from the nonescalator group and 3 from the escalators group dropped out of the follow-up trial at 3 months. Eight nonescalators and 7 escalators had hypertension. Diabetes was present in 2 nonescalators and 6 escalators. Baseline characteristics were not significantly different between the 2 groups. The mean age was 56.0±5.2 years in the nonescalator group and 58.8±5.0 years in the escalator group (p=0.056). PSA (mg/dL) was 2.0±2.4 among nonescalators and 1.5±1.0 in the escalators (p=0.299). Prostate size (g) was 28.7±15.0 in the nonescalator group and 27.2±9.9 in the escalator group (p=0.688).

The IIEF-5 scores; total IPSS; IPSS voiding, storage, and QoL subscores; and peak flow rates before and after treatment are compared between the escalators and nonescalators in Table 1. Compared with the nonescalators, the escalators had higher IPSS-storage scores at baseline (p=0.027) and week 4 (p=0.027), higher IPSS-total at week 4 (p=0.038), and lower IPSS-QoL scores at week 4 (p=0.016). Other IPSS parameters and IIEF-5 scores were not significantly different. The peak flow rates (mL/s) at baseline and week 12 were 13.6±4.6 and 15.9±4.4 in nonescalators and 12.7±5.1 and 13.9±5.2 in escalators, respectively. The peak flow rate improved from baseline values in both groups, but was not significantly different between the 2 groups.

The mean changes in the IIEF-5 score at weeks 4 and 12 were 0.56±2.18 and 1.50±2.10 in the nonescalator group and 0.95±2.15 and 3.26±3.07 in the escalator group, respectively. EF was significantly improved at week 12 in both groups, but was not significantly improved at week 4. There was a significant difference in IIEF-5 scores at week 12 between the escalators and nonescalators (3.2 vs. 1.5, p=0.023) (Fig. 1A). The degree of EF improvement (ΔIIEF-5 score) was positively associated with LUTS improvement, ΔIPSS-total (r=-0.458, p=0.004) (Fig. 1B), ΔIPSS-voiding (r=-0.432, p=0.008), ΔIPSS-storage (r=-0.380, p=0.011), and ΔIPSS-

TABLE 1. Changes in erectile function and lower urinary tract symptoms before and after treatment according to dose-escalation status

	Nonescalators (n=24)			Escalators (n=26)		
	Baseline	Week 4	Week 12	Baseline	Week 4	Week 12
IIEF-5	13.3±5.7	13.2±5.7	14.8±5.7	12.8±3.6	13.6±4.2	16.0±4.6
IPSS-TS[b]	15.8±4.3	11.0±4.7	8.8±4.7	17.8±6.9	15.0±7.9	10.0±8.8
IPSS-VS	10.4±3.6	6.7±3.3	5.5±3.2	10.7±5.1	8.9±5.0	5.7±5.6
IPSS-SS[a,b]	5.4±2.2	4.3±2.3	3.2±2.3	7.0±2.6	6.0±2.9	3.2±1.1
IPSS-QoL[b]	3.5±1.0	2.4±1.0	2.0±1.0	4.0±1.0	3.2±1.1	2.3±1.3
PFR (mL/s)	13.6±4.5		15.9±4.4	12.7±5.1		13.9±5.2

Values are presented as mean±standard deviation.
IIEF-5, International Index of Erectile Function-5; IPSS-TS, total International Prostate Symptom Score; IPSS-VS, IPSS-voiding score; IPSS-SS, IPSS-storage score; QoL, quality of life; PFR, peak flow rate.
$p < 0.05$ between nonescalators and escalators at baseline[a], week 4[b], and week 12[c].
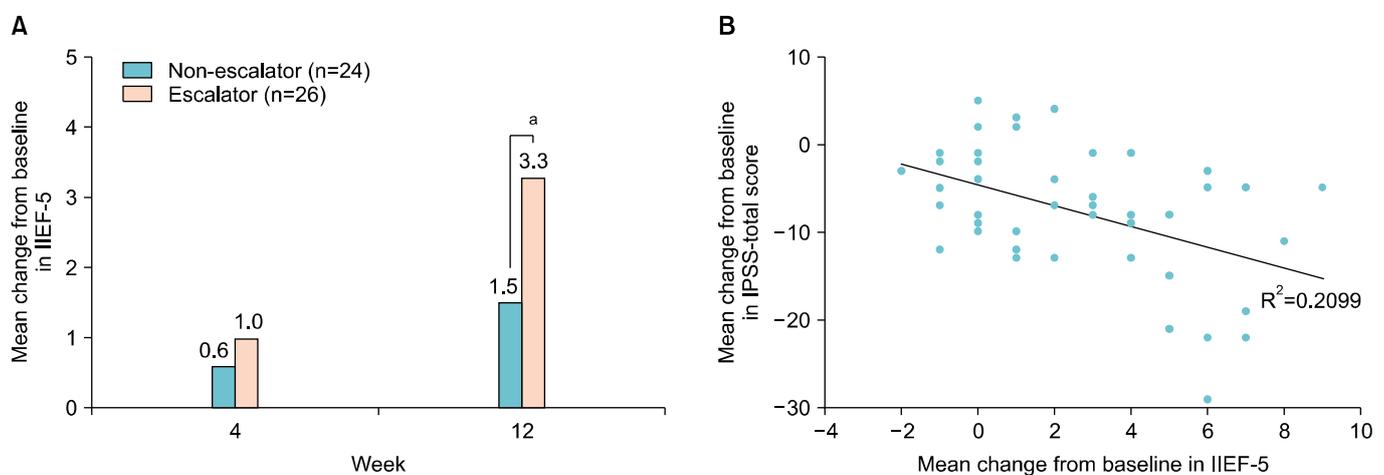
FIG. 1. Mean change from baseline outcome in scores of International Index of Erectile Function-5 (IIEF-5), (A) comparison considering treatment period ([a]:$p < 0.05$ for nonescalator vs. escalator at 12-week after treatment) and (B) correlation mean change from baseline to week 12 in International Prostate Symptom Score (IPSS)-total score with in IIEF-5 (Pearson r=-0.458, p=0.001).

QoL (r=-0.226, p=0.04), but not the change in peak flow rate (r=0.106, p=0.516). The difference in the IIEF-5 score between the 2 groups was not significant (1.2 for escalators vs. 0.8 for nonescalators, p=0.859) in 15 patients who showed no improvement of LUTS, and a statistically significant increase (4.6 for escalators vs. 1.7 for nonescalators, p=0.002) was observed in only 35 patients who had improved LUTS.

The mean changes at week 4 from baseline in the total IPSS and in the voiding, storage, and QoL subscores were -4.8±4.5, -3.7±3.9, -1.1±1.8, and -1.1±1.4 in the nonescalator group and -2.8±7.0, -1.8±5.4, -1.0±2.1, and -0.8±1.3 in the escalator group, respectively. Nonescalators achieved better improvement in IPSS-total and IPSS-voiding scores than did escalators, but the difference was not statistically significant. The mean changes in the total IPSS and in the voiding, storage, and QoL subscores at week 12 were -7.0±4.5, -4.8±3.8, -2.1±1.9, and -1.4±1.6 in the nonescalator group and -7.8±9.2, -5.0±6.8, -2.8±2.9, and -1.6±1.4 in the escalator group, respectively (Fig. 2). There was

also not a significant difference in the value of mean change between the 2 groups at week 12.

There were no serious adverse events requiring drug discontinuation in either group. Headache was reported in 1 patient and dizziness in 2 patients. Ejaculation disorder (reduced ejaculate, retrograde ejaculation, and anejaculation) was reported in 8 (33.3%) of 24 nonescalators and 10 (38.5%) of 26 escalators, but there was no significant difference between the 2 groups. Of patients with ejaculation problems, 3 patients (1 of the nonescalators and 2 of the escalators) complained of anejaculation or retrograde ejaculation, and the others had low ejaculated volume.

DISCUSSION

ED and LUTS are common urological diseases in adult men. Although the pathophysiological relationship between them is not clear, age is considered a strong risk factor because both diseases are more prevalent with increasing age, and their occurrence is affected by similar under-
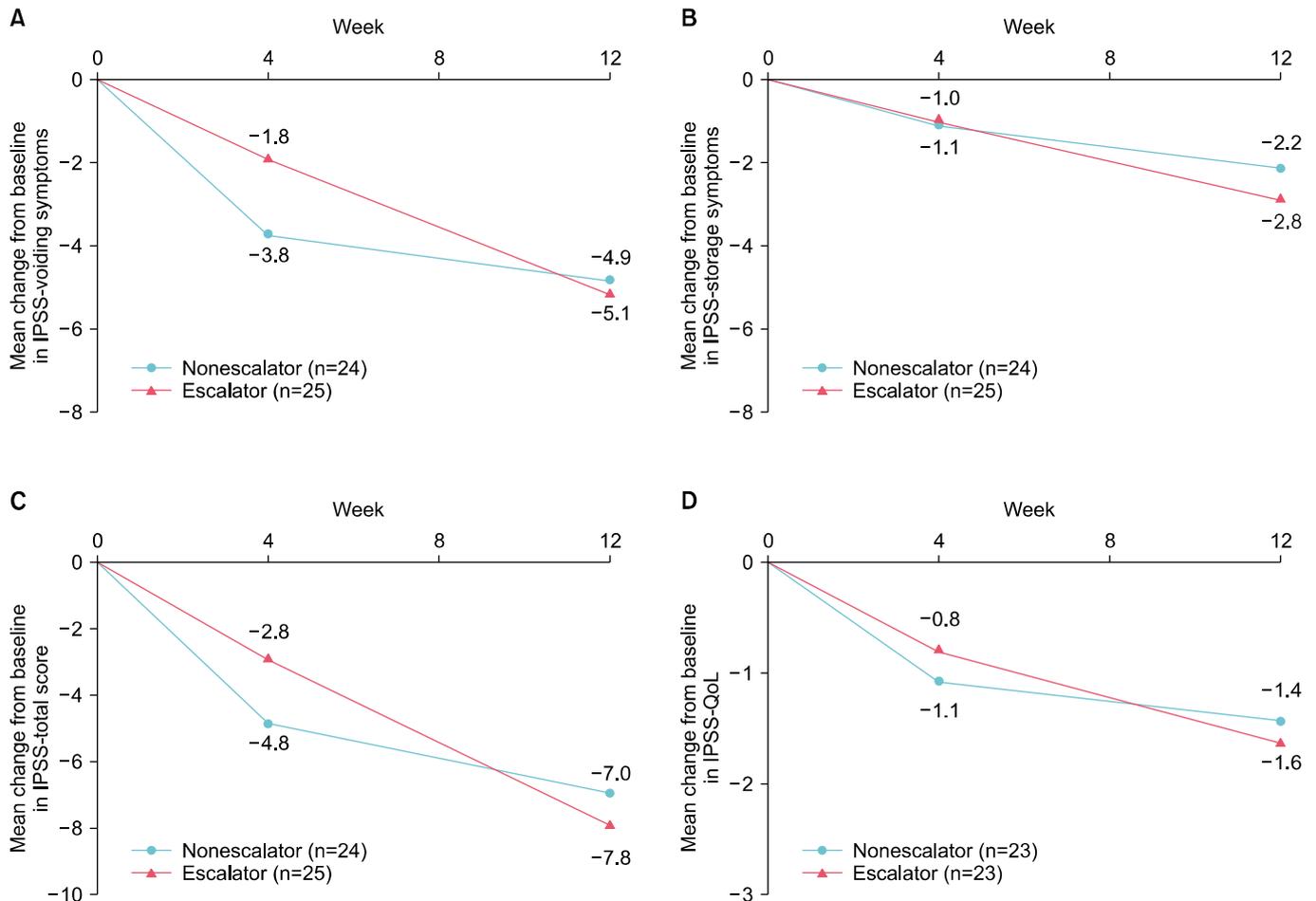
FIG. 2. Mean change from baseline in score of (A) International Prostate Symptom Score (IPSS)-voiding symptoms, (B) IPSS-storage symptoms, (C) IPSS-total score, and (D) IPSS-quality of life (QoL) on 4- and 12-week after tamsulosin treatment by escalation status (p>0.05 for nonescalator vs. escalator at week 4 and 12).

lying conditions: diabetes, hypertension, cardiovascular disease, obesity, dyslipidemia, pelvic ischemia, and limited activity related to the aging process [16,17]. Recent studies have reported that LUTS is independently related to ED with consideration of age-independent risk factors for the development of ED [17,18]. The prevalence of ED is significantly higher in the presence of both voiding and storage LUTS, particularly storage LUTS [19,20]. As previously mentioned, α1-AR antagonists have no negative effects on EF and their positive effect may be correlated to the improvement of LUTS. In addition, it has been reported that PDE5Is also have a positive effect on LUTS through the relaxation of the prostate and bladder neck. Thus, therapeutic trials for LUTS or for ED have been followed for indications of improvement in the other disease.

According to studies reporting a positive role of α1-AR antagonists on EF in men with LUTS and ED, Hofner et al. [21] suggested that overall improvement in QoL through successful treatment of LUTS might elicit improvement in EF. Van Moorselaar et al. [22] and Permpongkosol et al. [23] showed that long-term alfuzosin treatment improved sexual function, although not in men with

severe LUTS. They explained that the improvement of LUTS induced an improvement in QoL by reducing psychological stress and restoring self-image and that the improved QoL may have a direct effect on EF. Jung et al. [8] also showed that EF was improved only in patients in whom LUTS were treated by α1-AR antagonists and thus that the improvement in voiding symptoms and uroflow may be associated with the improvement in EF. Our study also showed that improvements in voiding and storage symptoms and in QoL were similar between the 2 groups and were significantly correlated with the improvement in EF. The improvement in EF was prominently observed in the patients who achieved improvement in LUTS. These findings suggest that improvement of LUTS may indirectly affect improvement of EF.

In a series regarding treatment with a combination of PDE5Is and α1-AR antagonists for ED patients, Tuncel et al. [24] indicated that the combination of sildenafil and tamsulosin was not superior to either drug alone for LUTS and ED and that improvement of EF with tamsulosin may be expected with the treatment of LUTS in men with LUTS and ED. On the other hand, Kaplan et al. [15] and Liguori

et al. [25] reported that the combination of alfuzosin and sildenafil or tadalafil was superior to monotherapy for LUTS and ED; however, those authors did not define the mechanism of the synergistic effect on both LUTS and ED owing to a lack of a placebo arm. Meanwhile, De Rose et al. [26] proposed that the addition of doxazosin for sildenafil-refractory ED patients resulted in a significant increase in the IIEF and that this synergistic effect may have been caused by a decrease of penile vasoconstrictive sympathetic tone by doxazosin enhancing the vasoactive effects of sildenafil. *In vitro*, the corpus cavernosum is relaxed by selective α1-AR antagonists in a concentration-dependent fashion and the combination of PDE5I and α1-AR antagonists is more efficient through direct effects on relaxing adrenergic tone or enhancing nitrergic relaxation [27,28]. These basic results may provide an explanation for the synergistic effect of the combination of PDE5Is and α1-AR antagonists in clinical trials and the possibility of dose-dependent effects of α1-AR antagonists on EF.

In our results, there were significant improvements in EF and LUTS in both groups at week 12, but compared with nonescalators, escalators did not achieve more improvements of LUTS, such as of storage and voiding symptoms and QoL. The only differences between the 2 groups were the mean change in the IIEF-5 score and drug dosage. The increase in the IIEF-5 score was two-fold higher in escalators (3.3) than in nonescalators (1.5). This comparative result may indicate that α1-AR antagonists contribute to the improvement of EF through a mechanism that may directly cause relaxation of the adrenergic tone of the corpus cavernosum in a dose-dependent fashion. However, this trial involved open-label and non-placebo controls, which can affect subjective outcome. Thus, the better improvement of EF in escalators should be considered a placebo effect.

Studies addressing the onset of efficacy of 0.2 to 0.4 mg tamsulosin showed that the total IPSS was maximally decreased at 4 weeks and later maintained [13,29]. On this basis, all patients in this study were given 0.2 mg tamsulosin for the initial 4 weeks and further administration of 0.2 mg or 0.4 mg for an additional 8 weeks was determined according to a discussion between the patient and a physician regarding the efficacy and tolerability of treatment for LUTS. The prevalence of dose escalation was 52% (26/50). Insufficient improvement of voiding symptoms may cause dose escalation, although the mean change in the IPSS voiding score was not significantly different between the 2 groups.

No patient discontinued treatment for an adverse event. The most common adverse event was abnormal ejaculation. Ejaculation disorder is reported to occur at a higher frequency during treatment with tamsulosin than during treatment with other α1-AR antagonists. The prevalence is 0% to 3.3% in Korean reports (0.2 mg/d) and 10% to 30% in Western studies (0.4 mg/d), with 90% being low ejaculatory volume and 35% being anejaculation (0.8 mg/d) [30]. The frequency of ejaculation disorder in this study was

33.3% for 0.2 mg tamsulosin and 38.5% for 0.4 mg. This is higher than in previous articles. The most likely reason may be a nocebo effect caused by the detailed explanation of side effects before prescription. Regardless, the three patients who described anejaculation or retrograde ejaculation were indifferent to it. The others reported a decrease of ejaculates. These observations suggest safety and tolerability in dose escalation to 0.4 mg.

Although this was a prospective study with a flexible dose, our study had limitations such as being open label, having no placebo arm, having no adjustment for comorbidities related to ED, and having a small size. Because of the dependency upon the patients' subjective points of view in the dose escalation decision, there was a slight lack of objectivity in the way the escalators were selected. However, this trial may be worthwhile as an initial study describing differences in improvement in EF according to α1-AR antagonist dose.

CONCLUSIONS

Dose escalation to 0.4 mg/d provided a near-competitive improvement in LUTS in patients refractory to treatment with 0.2 mg/d tamsulosin. The improvements in voiding symptoms, storage symptoms, and QoL were correlated with the improvement in EF. The increase in the IIEF-5 score was significantly higher in escalators, and this change was especially prominent in patients with successfully treated LUTS. These findings indicate that α1-AR antagonists may contribute to the improvement of EF through a mechanism that may indirectly cause improvement in LUTS and QoL as well as directly cause relaxation of the corpus cavernosum in a dose-dependent fashion. However, to elucidate our results, further large-scale, quantitative studies need to be pursued.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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