



Effect of Improvement in Lower Urinary Tract Symptoms on Sexual Function in Men: Tamsulosin Monotherapy vs. Combination Therapy of Tamsulosin and Solifenacin

Kyungtae Ko, Dae Yul Yang, Won Ki Lee, Sae Woong Kim¹, Du Geon Moon², Ki Hak Moon³, Nam Cheol Park⁴, Jong Kwan Park⁵, Hwan Cheol Son⁶, Sung Won Lee⁷, Jae Seog Hyun⁸, Kwangsung Park⁹

Department of Urology, Hallym University College of Medicine, Chuncheon, ¹The Catholic University College of Medicine, Seoul, ²Korea University College of Medicine, Seoul, ³Yeungnam University College of Medicine, Daegu, ⁴Pusan National University School of Medicine, Busan, ⁵Chonbuk National University Medical School, Jeonju, ⁶Seoul National University College of Medicine, Seoul, ⁷Sungkyunkwan University School of Medicine, Seoul, ⁸Gyeongsang National University School of Medicine, Jinju, ⁹Chonnam National University Medical School, Gwangju, Korea

Purpose: To evaluate how much the improvement of lower urinary tract symptoms (LUTS) affects sexual function and which storage symptoms or voiding symptoms have the greatest effect on sexual function.

Materials and Methods: A total of 187 patients were enrolled in this study. Patients were randomly assigned to receive either tamsulosin 0.2 mg (group A) or tamsulosin 0.2 mg and solifenacin 5 mg (group B). At 4 weeks and 12 weeks, the LUTS and sexual function of the patients were evaluated by use of the International Index of Erectile Function-5 (IIEF5), International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS) questionnaire, uroflowmetry, and bladder scan.

Results: Both groups A and B showed statistically significant improvements in IPSS, OABSS, and quality of life (QoL). Group A showed improved maximum flow rate, mean flow rate, and residual urine volume by time. Group B did not show an improvement in flow rate or residual urine volume but total voiding volume increased with time. The IIEF5 score was not improved in either group. In group A, the IIEF5 score dropped from 13.66±4.97 to 11.93±6.14 after 12 weeks (p=0.072). Group B showed a decline in the IIEF5 score from 13.19±5.91 to 12.45±6.38 (p=0.299). Although group B showed a relatively smaller decrease in the IIEF5 score, the difference between the two groups was not significant (p=0.696).

Conclusions: Tamsulosin monotherapy and combination therapy with solifenacin did not improve erectile function despite improvements in voiding symptoms and QoL. The improvement in storage symptoms did not affect erectile function.

Keywords: *Erectile dysfunction; Lower urinary tract symptoms; Overactive urinary bladder*

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Corresponding Author:

Kwangsung Park
Department of Urology,
Chonnam National University
Hospital, Chonnam National
University Medical School, 42
Jebong-ro, Dong-gu, Gwangju
501-757, Korea
TEL: +82-62-220-6701
FAX: +82-62-227-1643
E-mail: kpark@chonnam.ac.kr

INTRODUCTION

Lower urinary tract symptoms (LUTS) and sexual dysfunction are frequently observed in aged men. Large-scale epidemiologic studies have reported that LUTS are closely

and independently associated with sexual dysfunction [1]. Through the relieving of LUTS, α -blockers result in improvement of sexual dysfunction [2,3]. Theoretically, modulation of α -adrenergic activity, which decreases smooth muscle tone in the bladder neck, prostate capsule, and cor-

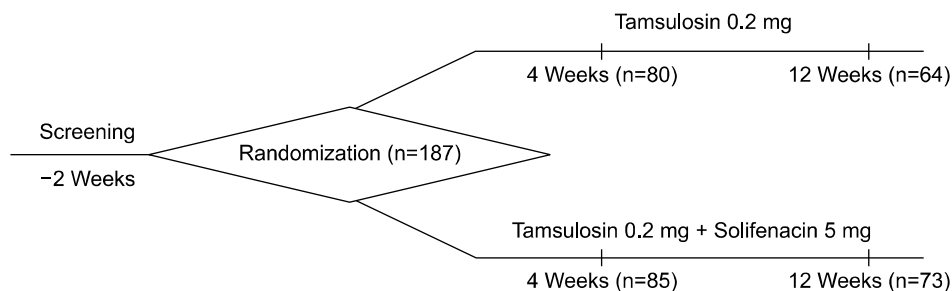


FIG. 1. Flow of the study.

pus cavernosum, may improve LUTS and sexual dysfunction at the same time. By contrast, as the result of a blood pressure lowering effect or another uncertain mechanism, α -blockers may have an adverse effect on erectile function [4]. The results of our recent study suggested that tamsulosin 0.2 mg did not exhibit any significant effect on sexual function [5].

Storage symptoms such as urgency, urge incontinence, and nocturia are more bothersome than voiding symptoms [6]. Anticholinergics are an effective medication for overactive bladder (OAB) with urgency and with or without urge incontinence. A recent study reported that anticholinergics and α -blocker combination therapy was effective for patients with benign prostatic hyperplasia and OAB [7,8]. However, the relationship between storage symptoms and sexual dysfunction is not well known. Knowing the effect of storage symptoms on sexual dysfunction would allow for more valuable management of sexual dysfunction.

In this study, we evaluated how much the improvement of LUTS affects sexual function and which storage symptoms or voiding symptoms have the greatest effect on sexual function as assessed by the International Prostate Symptom Score (IPSS), overactive bladder symptoms score (OABSS), and International Index of Erectile Function (IIEF) questionnaires.

MATERIALS AND METHODS

A total of 187 patients were enrolled in this multicenter, prospective, randomized, comparative, open-label study from July 2011 to June 2012. The primary purpose of this study was to evaluate the effect of treatment of LUTS on patients with sexual dysfunction. The second purpose was to assess which voiding symptoms or storage symptoms most affected sexual dysfunction. The Ethic Committee of each participatory institution approved this clinical study, and written consent was provided by all subjects prior to participation (11-008).

Men 40 years of age or older who had LUTS as indicated by an IPSS > 12, urinary frequency ($\geq 8/d$), urgency ($\geq 1/d$), and symptoms on a 3-day voiding diary were invited to participate. All patients were sexually active more than once per month regardless of IIEF score. Patients with urologic malignancy, urinary tract infection, medical renal disease, medical liver disease, or clinically significant blad-

der outlet obstruction (residual urine > 100 mL) were excluded from study. Patients who took medications such as androgens, antiandrogens, and phosphodiesterase type 5 inhibitors were also excluded. All patients provided informed consent.

Initially, patients were evaluated by history taking, physical examination, urine analysis with microscopic assay, uroflowmetry (UFM), bladder scan, voiding diary, IIEF, IPSS, and OABSS questionnaires. Patients were randomly assigned to receive either tamsulosin 0.2 mg only (group A) or tamsulosin 0.2 mg and solifenacin 5 mg combination (group B) by block randomization. At 4 weeks and 12 weeks, the LUTS and sexual function of the patients were evaluated by the IIEF, IPSS, and OABSS questionnaire. UFM and bladder scan were performed for functional study (Fig. 1).

Clinicopathologic variables between the two groups were statistically analyzed by use of two-sample t-tests. Mixed model analysis was performed to compare the outcomes of each group. SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. In all tests, p-values of 0.05 were considered statistically significant.

RESULTS

A total of 187 patients were registered for this study. Group A consisted of 93 patients and group B consisted of 94. Twenty-two patients dropped out at the 4-week follow-up (group A, 13 patients; group B, 9 patients), and 28 patients dropped out at the 12-week follow-up (group A, 16 patients; group B, 12 patients). Overall, 64 patients (68.8%) in group A and 73 patients (77.7%) in group B completed this study. The baseline clinicopathologic data are shown in Table 1.

The mean age of the enrolled patients (n=187) was 61.09 ± 9.18 years. Mean prostate volume and PSA were 28.71 ± 11.13 mL and 1.55 ± 1.78 ng/dL, respectively. UFM study showed a total voiding volume of 262.02 mL, mean flow rate of 7.43 mL/s, and maximum flow rate (Q_{max}) of 14.6 mL/s. Residual urine checked by bladder scan was 25.26 mL. Mean IPSS was 19.40 ± 5.91 (voiding symptoms, 11.08 ± 4.58 ; storage symptoms, 8.02 ± 2.91). Mean OABSS, quality of life (QoL), and IIEF scores were 6.73 ± 2.61 , 4.10 ± 0.95 , and 13.14 ± 5.77 , respectively. No clinicopathologic factors were significantly different between the two groups except the OABSS, which was higher in group B than in group A (6.32 vs. 7.13, $p=0.037$) (Table 1).

TABLE 1. All clinicopathologic factors were not different between two groups except OABSS

Variable	Overall (n=187)	Group A (n=93)	Group B (n=94)	p-value
Age (y)	61.09±9.18	61.22±8.97	60.96±9.43	0.849
BMI (kg/m ²)	23.97±2.30	23.94±2.34	23.96±2.27	0.896
PSA (mg/mL)	1.55±1.78	1.41±1.16	1.69±2.25	0.693
TRUS	28.71±11.13	28.90±11.36	28.52±10.96	0.764
Qmax (mL/s)	14.60±5.74	14.39±5.67	14.80±5.86	0.708
Mean flow	7.43±3.15	7.14±3.21	7.45±3.12	0.848
Voiding volume	262.03±113.62	273.69±108.87	250.70±117.90	0.151
R/U	25.26±26.44	24.73±27.48	25.77±25.54	0.437
IIEF5	13.14±5.77	13.08±5.63	13.19±5.95	0.891
OABSS	6.73±2.61	6.32±2.32	7.13±2.82	0.037*
IPSS_total	19.40±5.91	19.07±5.99	19.62±5.86	0.618
IPSS_storage	8.02±2.91	7.77±2.91	8.27±2.91	0.245
IPSS_voiding	11.08±4.58	11.22±4.53	10.95±4.65	0.685
QoL	4.10±0.94	3.98±2.01	4.22±0.86	0.089

Values are presented as mean±standard deviation.

OABSS, overactive bladder symptom score; BMI, body mass index; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; Qmax, maximum flow rate; R/U, residual urine; IIEF5, International Index of Erectile Function-5; IPSS, International Prostate Symptom Score; QoL, quality of life.

Group A: tamsulosin 0.2 mg only. Group B: tamsulosin 0.2 mg+solifenacin 5 mg.

UFM study showed the Qmax, mean flow rate, and residual urine volume improved with time in group A. Group B did not show an improvement in flow rate or residual urine volume with time, whereas total voiding volume did increase. Overall, groups A and B did not differ significantly in UFM scale (Qmax, $p=0.404$; mean flow rate, $p=0.179$; voiding volume, $p=0.677$) (Fig. 2). Because residual urine volume did not decrease, group B showed a greater residual urine volume than that in group A ($p=0.013$).

In the questionnaire analysis of LUTS, both groups showed statistically significant improvement in the IPSS, OABSS, and QoL. When the IPSS was divided into storage and voiding symptoms, both groups showed significant improvement in both categories of symptoms. However, the difference between the two groups was not significant ($p=0.083$ and $p=0.358$) (Fig. 3). The OABSS was higher in group B than in group A at baseline ($p=0.037$). However, after treatment for 12 weeks, there was no significant difference in the OABSS in either group ($p=0.905$, data not shown).

The IIEF5 score was not improved in either group (Fig. 4). In group A, the IIEF5 score dropped from $13.66±4.97$ to $11.93±6.14$ after 12 weeks of medication ($p=0.072$). Group B also showed a decline in the IIEF5 score (from $13.19±5.91$ to $12.45±6.38$, $p=0.299$). Although group B showed a relatively smaller decrease in the IIEF5 score compared with group A, the difference between the two groups was not statistically significant ($p=0.696$).

Adverse effects were reported for 15 patients. In group A, six patients complained of mild adverse effects (gastric discomfort in 5, dry mouth in 1). These mild adverse effects resolved in all patients without any management. Nine patients in group B had a mild adverse effect (gastric dis-

comfort in 3, itching in 1, dry mouth in 2, general weakness in 1, constipation in 1, and urticaria in 1). Patients with urticaria took a dermatologic medicine. The combination group showed more adverse effects, but urinary retention was not reported in the study period.

DISCUSSION

The Multinational Survey of the Aging Male suggested that LUTS were an independent prognostic factor for sexual dysfunction [9]. LUTS medication improves the sexual dysfunction of LUTS patients [2,3]. However, LUTS are divided into voiding symptoms and storage symptoms. α -Blockers and 5-androgen receptor inhibitors are an effective medication for men with LUTS [10,11]. However, these medications are not sufficient for managing all patients with LUTS, because LUTS originate not only from pathologic benign prostatic hyperplasia also as a result of a detrusor muscle condition [12]. Several studies have reported that OAB is highly associated with male sexual dysfunction [13-15].

Storage symptoms such as frequency, nocturia, urgency, and urge incontinence are more common and bothersome than voiding symptoms such as weak stream, intermittency, hesitancy, strain, and postvoid dribbling [6]. A previous study reported that 51% of LUTS patients have storage symptoms and 26% have voiding symptoms at age ≥ 18 years, and 74% of patients have storage symptoms and 37% have voiding symptoms at age ≥ 60 years [16]. Other studies showed that 28% of men aged ≥ 40 years had LUTS. Storage symptoms only (13%) was more frequent than voiding symptoms only (6%). Mixed symptoms (9%) were more frequent than voiding symptoms, too [17]. Thus, α -blocker monotherapy may not be the appropriate treat-

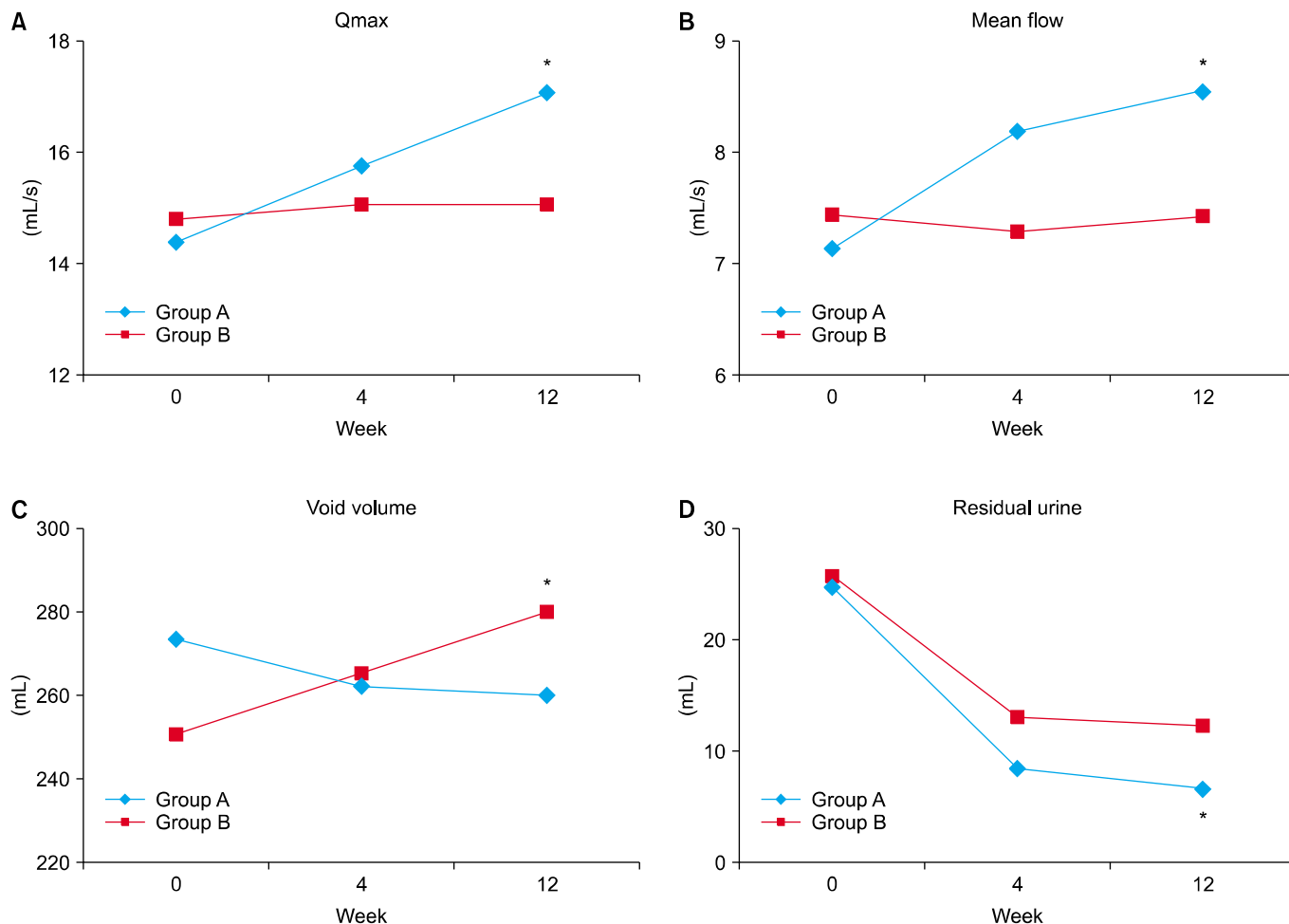


FIG. 2. (A-C) The groups did not differ significantly on variables of the uroflowmetry scale except for residual urine volume. (D) Because residual urine volume did not decrease, group B showed a much greater residual urine volume than that in group A ($p=0.013$). Group A: tamsulosin 0.2 mg only. Group B: tamsulosin 0.2 mg+solifenacin 5 mg. *Statistically significant by time ($p<0.05$).

ment in patients with LUTS including OAB because of failure to relieve the storage symptoms. In a previous study, the combination treatment of α -blocker and anticholinergic was a safe and effective modality in LUTS patients with OAB [8]. However, it has not been sufficiently evaluated whether anticholinergic monotherapy or combination therapy with an α -blocker and an anticholinergic improves sexual function in LUTS patients with OAB. In this study, although not statistically significant, the IIEF score of the combination therapy group decreased relatively less than in the monotherapy group.

In a recent previous study of initial combination treatment with tamsulosin 0.2 mg and solifenacin 5 mg, the authors reported that earlier combination treatment improves storage symptoms and QoL [7]. Their clinicopathologic data and results were very similar to ours. Their data showed that the combination group had an improved IPSS storage score, QoL, and OABSS at 4 weeks, but that there was no significant difference in any of the questionnaire scores between the two groups in 12 weeks. Additionally, they reported that the measured UFM values did not differ

statistically between the two groups. We checked UFM variables and bladder scans in this study, also. In contrast with the questionnaire, the values measured by UFM gave us some important information. The combination group showed increased voiding volume with time (250.7 mL at baseline, 265.5 mL at 4 weeks, 279.6 mL at 12 weeks, $p=0.019$), whereas flow rate and residual urine volume did not change. In another study also, the combination of tamsulosin 0.4 mg and solifenacin 6 mg/9 mg did not affect the uroflow rate or residual urine [18]. The lack of change in residual urine volume in group B directly affected the lack of occurrence of urinary retention in this study.

The subscale numbers 1, 3, 5, and 6 of the IPSS imply voiding symptoms and the numbers 2, 4, and 7 imply storage symptoms. The storage subscale of IPSS included urgency but not urge incontinence. Thus, we also used the OABSS. At baseline, although the storage symptom score was not significantly different, group B had a higher OABSS than group A. This difference may be because of reference to different symptom durations on the questionnaires. The IPSS asks about voiding symptoms during

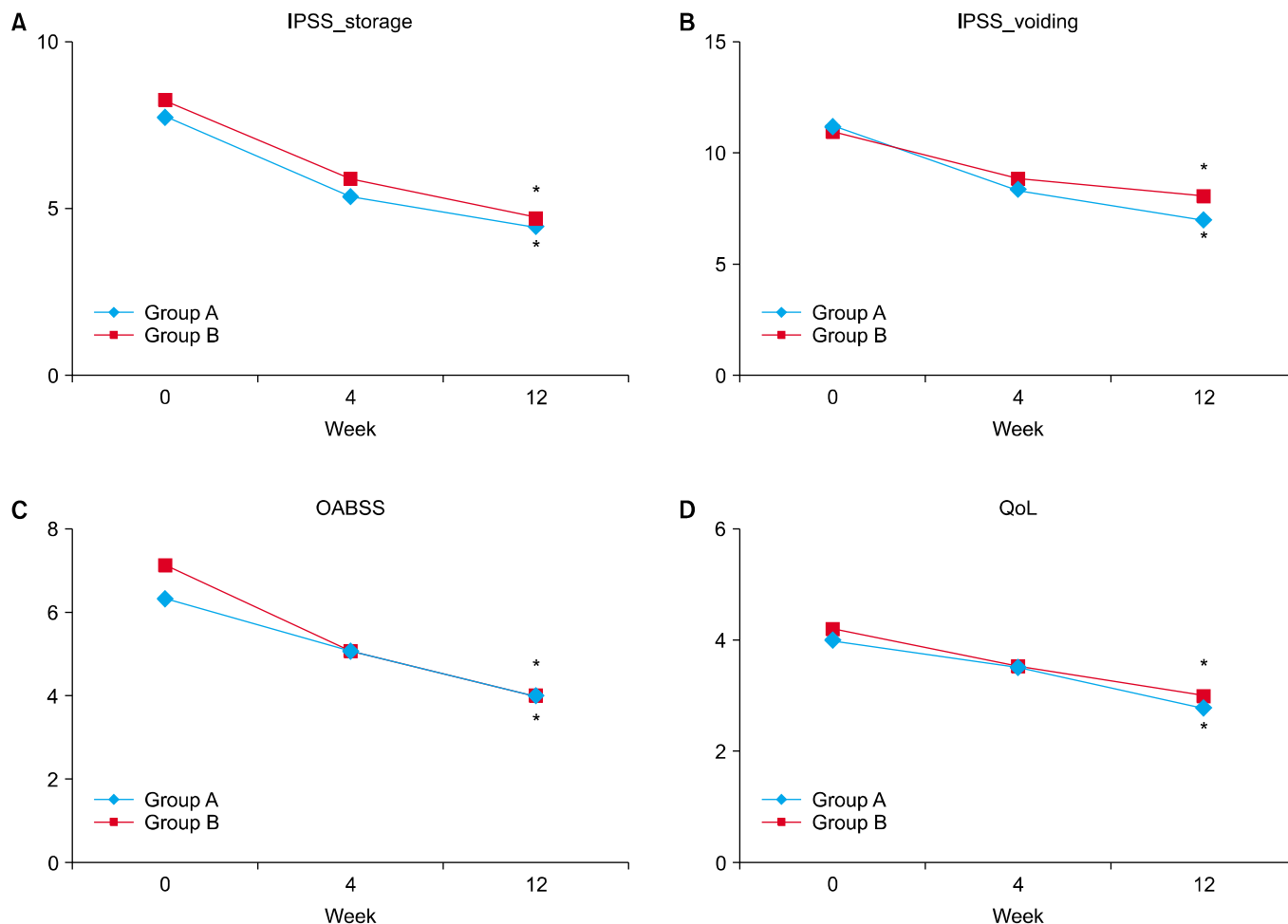


FIG. 3. Both groups showed a statistically significant improvement in the International Prostate Symptom Score (IPSS), overactive bladder symptom score (OABSS), and quality of life (QoL) score. However, a statistically significant difference was not observed between the two groups. Group A: tamsulosin 0.2 mg only. Group B: tamsulosin 0.2 mg+solifenacin 5 mg. *Statistically significant by time ($p < 0.05$).

the last month in contrast with the last week on the OABSS. Second, the question about frequency is quite different: “How often have you had to urinate less than every two hours?” on the IPSS vs. “How many times do you typically urinate from waking in the morning until sleeping at night?” on the OABSS [19,20]. Frequency (question 1) and nocturnal frequency (question 2) on the OABSS were statistically higher in group B ($p=0.059$, $p=0.008$, Mann-Whitney test, data not shown). Urgency (question 3) was not significantly different ($p=0.533$). The mean number of instances of urge incontinence (question 4) was 0.91 in group A and 1.11 in group B. This difference was also not statistically significant ($p=0.568$).

It is well known that OAB has a greater negative impact on everyday life and a detrimental effect on sexual life in women [21]. Anticholinergics improve sexual function in female patients with OAB [22,23]. The mechanism by which anticholinergics affect sexual function differs substantially between men and women. Investigators have suggested that the occurrence of urinary leakage during in-

tercourse may be stressful in women, and anticholinergics may improve sexual function by aborting urinary leakage [22]. However, the detrusor muscle and sexual function are regulated by a shared neurologic nerve pathway and neurotransmitters [23]. Thus, anticholinergics including solifenacin may indirectly affect the sexual function of both men and women. In our study, a direct comparison between anticholinergics and an α -blocker or placebo was lacking because there was no solifenacin only treatment group. This study showed that sexual function improved regardless of solifenacin. To understand the effect of anticholinergics on sexual function in men, additional study including a solifenacin only treatment group will be necessary.

This study had several limitations. First, a difference in follow-up loss was present among the centers, and group B showed a higher OABSS at baseline. This may indicate a selection bias even though this was a prospective study. However, the clinicopathologic data in this study were similar to previous studies, and other data were well dis-

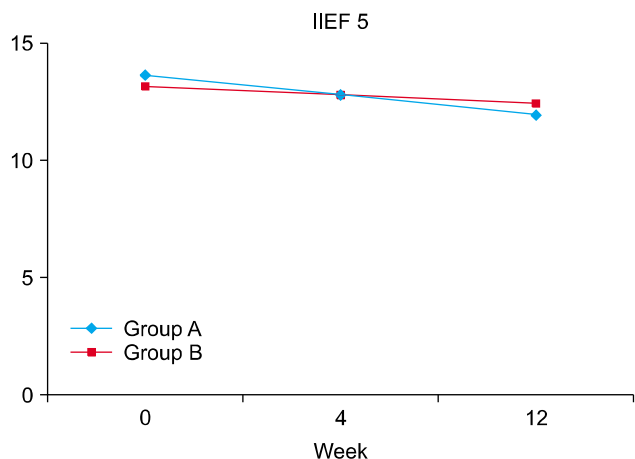


FIG. 4. Neither group of patients with lower urinary tract symptoms showed an improvement in sexual dysfunction. Although the International Index of Erectile Function-5 (IIEF5) score decreased relatively less in group B compared with group A, the difference between the two groups was not statistically significant ($p=0.696$). Group A: tamsulosin 0.2 mg only. Group B: tamsulosin 0.2 mg+solifenacin 5 mg.

tributed between the two groups. Data were collected from patients who completed the study. Second, tamsulosin is reported to result in de novo ejaculatory discomfort in about 10% of patients [5]. Ejaculatory discomfort is an important sexual problem. However, this topic was not addressed in the present study. Third, this study did not include a placebo group or solifenacin monotherapy group. If male OAB patients without bladder outlet obstruction are treated by anticholinergics, improved sexual function may be observed as in female patients with OAB. Last, due to the relatively short follow-up duration and small patient number, the results of this study should be interpreted cautiously.

CONCLUSIONS

Tamsulosin monotherapy and combination therapy with tamsulosin and solifenacin did not improve erectile function in LUTS patients. The improvement of storage symptoms was not significantly associated with sexual function.

CONFLICTS OF INTEREST

I (Kwangsung Park, corresponding author including other authors) got grants from Astellas Pharma Korea, Inc. However, Astellas Pharma Korea, Inc only had a financial role for this research.

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