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Efficacy of an Alpha-Blocker for the Treatment of Nonneurogenic Voiding Dysfunction in Women: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial

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Purpose: To evaluate the efficacy of an alpha-1 adrenergic receptor (α1-AR) blocker for the treatment of female voiding dysfunction (FVD) through a pressure-flow study.
Methods: This was a randomized, double-blind, placebo-controlled trial. Women aged ≥18 years with voiding symptoms, as defined by an American Urological Association symptom score (AUA-SS) ≥15 and a maximum flow rate (Qmax) <15 mL/sec with a voided volume of >100 mL and/or a postvoid residual (PVR) volume >150 mL, were randomly allocated to either the alfuzosin or placebo group. After 8 weeks of treatment, changes in the AUA-SS, Bristol female lower urinary tract symptoms (BFLUTS) questionnaire, Qmax/PVR, and voiding diary were compared between groups. Patients' satisfaction with the treatment was compared. Patients were categorized into 3 groups according to the Blaivas-Groutz bladder outlet obstruction (BOO) nomogram: none, mild, and moderate to severe. Subgroup comparisons were also made.
Results: Of a total of 187 women, 154 (79 alfuzosin, 75 placebo) were included in the analysis. After 8 weeks of treatment, the AUA-SS decreased by 7.0 in the alfuzosin group and by 8.0 in the placebo group. Changes in AUA-SS subscores, BFLUTS (except the I-sum), the voiding diary, and Qmax/PVR were not significantly different between groups. Approximately 54% of the alfuzosin group and 62% of the placebo group were satisfied with the treatment. No significant difference was observed between groups according to the presence or grade of BOO.
Conclusions: Alfuzosin might not be more effective than placebo for treating FVD. The presence or the grade of BOO did not affect the results. A further study with sufficient power is needed to determine the efficacy of α1-AR blockers for the treatment of FVD.

Keywords: Adrenergic alpha-antagonists; Bladder outlet obstruction; Female; Urodynamics

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INTRODUCTION

The International Continence Society and International Urogynecological Association have defined voiding dysfunction in females as abnormally slow and/or incomplete micturition diagnosed based on symptoms and urodynamic investigations [1]. The prevalence has been reported to range from 3% to 39% [2-5]. The most likely reason for this wide variation in the prevalence is the absence of standardized diagnostic criteria. There are no treatment guidelines, and the pathophysiological mechanisms are poorly understood.

Voiding-phase dysfunction may be caused by bladder and/or urethral factors. The causes related to the bladder include detrusor underactivity or acontractile detrusor, while the urethral causes include anatomical or functional bladder outlet obstruction (BOO). At the moment, no pharmaceutic agent capable of effectively enhancing detrusor contractility has been identified. However, alpha-1 adrenergic receptor (α1-AR) blockers improve urinary flow by increasing the relaxation of smooth muscles in the prostate and bladder neck. Thus, α1-AR blockers are the first-line treatment for benign prostate obstruction (BPO). Since voiding ability is relative to bladder contractility and outflow resistance, the reduction of urethral resistance by α1-AR blockers can reduce the required detrusor work and may improve urinary flow [6]. There are 3 subtypes of α1-ARs: α1A, α1B, and α1D. In the urethra, α1A is most prominent, while the detrusor muscle and bladder neck express mainly the α1D subtype. It is generally assumed that α1-AR blockers affect not only urinary smooth muscles, but also influence sympathetic, parasympathetic, and somatic nerves through the spinal cord, ganglia, and nerve terminals [7]. These nonprostate effects have led α-blockers to be considered as a possible treatment for women with voiding-phase dysfunction.

A few clinical trials have evaluated the efficacy of selective or non-selective α1-AR blockers in women [8-10]. These trials showed a positive effect in the treatment of female voiding dysfunction. However, the inclusion criteria and diagnoses were diverse, and they did not include a pressure-flow study, which is the key assessment for evaluating bladder outlet or detrusor function in the voiding phase.

Herein, we conducted a randomized, double-blind, placebo-controlled trial to compare the efficacy of an α1-AR blocker, alfuzosin (ALF) (Xatral XL, Sanofi-Aventis Korea marketed by Handok Pharmaceuticals Co., Ltd., Seoul, Korea), with placebo (PLA) for the treatment of female voiding dysfunction in a pressure-flow study.

MATERIALS AND METHODS

Study Design

This was a phase II, randomized, double-blind, placebo-controlled trial conducted at 9 university hospitals. Written informed consent was obtained from all participants before screening. The Institutional Review Board of each center approved the study, which is registered at http://clinicaltrials.gov (ClinicalTrials.gov ID; NCT00679315).

Study Participants

Females aged ≥18 years with a chief complaint of voiding symptoms for more than 3 months were screened in terms of demographics, medical history, surgical history, concomitant medications, pelvic exam, urinalysis (when women had a positive urinalysis suggestive of urinary tract infection, a urine culture was performed), American Urological Association symptom score (AUA-SS) [11], and the ratio of maximum flow rate (Qmax) to postvoid residual (PVR) volume. Women with an AUA-SS ≥15 and a Qmax <15 mL/sec with a voided volume of >100 mL and/or a PVR >150 mL in a noninvasive uroflowmetry study were included in the study. Participants were further evaluated with the Bristol female lower urinary tract symptoms (BFLUTS) questionnaire [12,13], patient perception of bladder condition (PPBC) survey [14], a 3-day voiding diary, and a pressure-flow study. Patients were categorized into 3 groups according to the female BOO nomogram proposed by

Blaivas and Groutz [15]: no BOO, mild BOO, or moderate to severe BOO. Women with urodynamic BOO underwent urethral calibration using a 16F female sound. If any resistance was found, the patient was considered to have anatomical BOO and was excluded from the study. Other exclusion criteria were history of surgery related to incontinence or cystocele, pelvic organ prolapse with pelvic organ prolapse quantification stage ≥3, clinically significant stress urinary incontinence proven by a cough test, neurogenic voiding dysfunction, recurrent urinary tract infections (≥4 times/yr), and pregnancy or nursing. When women had a urinary tract infection at screening, they were allowed to enroll after the infection was treated. Medications affecting lower urinary tract function (any other alpha-blocker besides alfuzosin, any cholinergic or anticholinergic drugs, or any drug for overactive bladder) were not permitted from 14 days before screening and throughout the study.

Randomization and Blinding

Eligible patients were randomly assigned to either the ALF (10 mg; Xatral XL) or PLA group at a 1:1 ratio. The randomization list was made according to a random permuted block design with a block size of 4 by center. The coding system did not permit undetectable breaks of the blinding except in a medical emergency.

Assessments

The primary endpoint was the difference between the ALF and PLA groups in the change of the total AUA-SS after 8 weeks of treatment. After 4 and 8 weeks of treatment, changes in AUA-SS, Qmax/PVR, BFLUTS scores, PPBC, and the voiding diary were compared between groups. Patients' perceptions of treatment benefit, satisfaction, and willingness to continue (BSW) were also compared. Those comparisons were also made in subgroups defined according to the presence and grade of BOO, as assessed according to the Blaivas-Groutz BOO nomogram.

Sample Size Determination

For a difference of 2.0 in the change of the total AUA-SS between the 2 groups from baseline to 8 weeks, 122 patients per group were required, with a significance level of 5% and power of 80% [16].

Statistical Analysis

Analysis was performed within the intention-to-treat (ITT) population. The ITT population included subjects who received at least 1 dose of the assigned drug and had data for the primary variable at baseline and at 8 weeks or the last observation. The last observation carried forward method was applied for missing data. To compare changes in the continuous variables within each group, the paired t-test or Wilcoxon signed-rank test was performed according to the normality of the distribution. For ordinal or nominal variables, the generalized estimating equation was used. To compare differences in the changes between groups, the t-test or Mann-Whitney test was performed for continuous variables and the generalized estimating equation was used for ordinal or nominal variables. The Bonferroni correction was applied as needed. SAS ver. 9.1.3 (SAS Institute Inc., Cary, NC, USA) was used, and P-values of <0.05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

Of a total of 187 (97 ALF, 90 PLA) women randomized to the 2 groups, 134 (66 ALF, 68 PLA) completed the study and 154 (79 ALF, 75 PLA) were included in the ITT analysis (Fig. 1). Their mean age was 57.7 (standard deviation [SD], ±11.6) years, and the mean symptom duration was 36 months. The mean total AUA-SS was 23.2 (±5.6), the storage score was 8.9 (±3.3), and

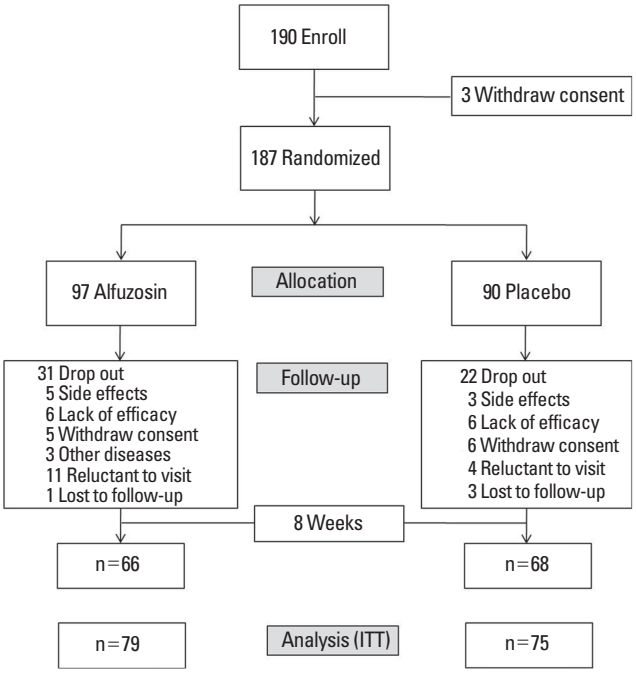

Fig. 1. Patient flow. ITT, intention-to-treat.

Table 1. Baseline characteristics of the intention-to-treat population

Variable	Alfuzosin (n=79)	Placebo (n=75)	P-value
Age (yr)	57.4±10.6	57.9±12.6	0.768[a]
Body mass index (kg/m^2)	23.1 (21.5–24.4)	23.4 (21.3–25.4)	0.753[b]
Symptom duration (mo)	36.0 (12.0–72.0)	36.0 (12.0–60.0)	0.339[b]
AUA-SS			
Total	23.0 (18.0–28.0)	22.0 (18.0–27.0)	0.323[b]
Storage	9.0 (7.0–12.0)	9.0 (6.0–11.0)	0.529[b]
Voiding	15.0 (11.0–17.0)	14.0 (11.0–18.0)	0.802[b]
Bother score	5.0 (4.0–6.0)	5.0 (4.0–5.0)	0.770[b]
BOO grade			0.144[c]
No	17/75 (22.7)	9/68 (13.2)	
Mild	43/75 (57.3)	47/68 (69.1)	
Moderate	12/75 (16.0)	12/68 (17.6)	
Severe	3/75 (4.0)	0/68 (0)	
Qmax (mL/sec)	9.9 (8.3–12.3)	11.3 (9.6–12.8)	0.041[b]
VV (mL)	181.0 (128.5–262.0)	169.0 (129.1–242.8)	0.608[b]
PVR (mL)	24.0 (2.0–95.0)	21.5 (8.0–100)	0.635[b]

Values are presented as mean±standard deviation or median (interquartile range).
AUA-SS, American Urological Association symptom score; BOO, bladder outlet obstruction; Qmax, maximum flow rate; VV, voided volume; PVR, postvoid residual.
[a]t-test; [b]Mann-Whitney test; [c]Chi-square test.

the voiding score was 14.4 (±3.8). The bother score was 4.8 (±0.8). Of the 143 women who underwent a multichannel urodynamic study, 82% (117 of 143) had BOO. There were no significant differences in demographic data, symptom and bother scores (AUA-SS, BFLUTS, PPBC), voiding diary data, distribution of BOO grade, or PVR between groups. The Qmax was significantly lower in the ALF group (9.9 mL/sec) group than in the PLA group (11.3 mL/sec). Comparisons of the baseline clinical characteristics between groups are summarized in Table 1.

Overall Patients

Within-group comparison between baseline and the end of treatment

After 8 weeks of treatment, the AUA-SS (total, storage, voiding, bother), BFLUTS (F-sum, V-sum), and PPBC improved significantly in both groups (Table 2, Fig. 2). Daytime- and 24-hour micturition episodes decreased significantly in both groups. The Qmax increased and the PVR decreased significantly in both groups (Table 2).

Between-group comparison of changes in the primary and secondary endpoints

The total AUA-SS decreased by 7 in the ALF group and 8 in the PLA group (P=0.788). The median changes in the storage scores were -2.5 (ALF) and -3.0 (PLA) (P=0.932), the median changes in the voiding scores were -4.5 (ALF) and -5.0 (PLA) (P=0.837), and the median changes in the bother scores were -1.0 (ALF) and -1.0 (PLA) (P=0.968).

The changes in BFLUTS (except the BFLUTS I-sum), PPBC,

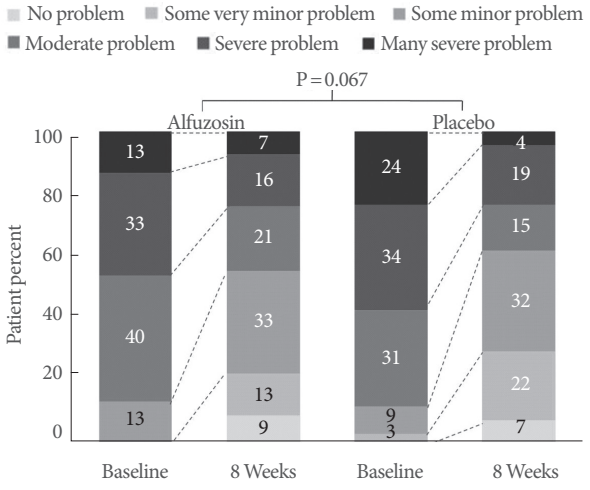

Fig. 2. Difference in PPBC changes. PPBC, patient perception of bladder condition.

Table 2. Changes in the efficacy parameter of the changes in efficacy parameters

Variable	Alfuzosin (n=79)			Placebo (n=75)			P-value
	Baseline	8 Weeks	Change	Baseline	8 Weeks	Change	
AUA-SS							
Total	23.0 (18.0–28.0)	14.0 (9.0–21.0)	-7.0 (-14.0 to -3.0)[d]	22.0 (18.0–27.0)	14.0 (9.0– 22.0)	-8.0 (-12.0 to -2.0)[d]	0.788[b]
Storage	9.0 (7.0–12.0)	6.0 (3.0–9.0)	-2.5 (-5.0 to 0)[d]	9.0 (6.0–11.0)	6.0 (3.0– 9.0)	-3.0 (-5.0 to 0)[d]	0.932[b]
Voiding	15.0 (11.0–17.0)	8.0 (5.0–12.0)	-4.5 (-10.0 to -2.0)[d]	14.0 (11.0– 18.0)	9.0 (5.0–13.0)	-5.0 (-9.0 to -2.0)[d]	0.837[b]
Bother score	5.0 (4.0–6.0)	4.0 (3.0–5.0)	-1.0 (-2.0 to 0)[d]	5.0 (4.0–5.0)	3.0 (3.0– 5.0)	-1.0 (-2.0 to 0)[d]	0.968[b]
BFLUTS							
F-sum	6.0 (5.0–8.0)	5.0 (4.0–7.0)	-1.0 (-3.0 to 1.0)[d]	6.0 (5.0–8.0)	5.0 (4.0–7.0)	-1.0 (-3.0 to 0)[d]	0.723[b]
V-sum	6.3 ± 3.1	4.0 ± 3.1	-2.3 ± 2.9[d]	6.3 ± 3.4	4.1 ± 3.1	-2.1 ± 3.5[d]	0.751[a]
I-sum	1.0 (0–4.0)	1.5 (0–3.0)	0.0 (-1.0 to 1.0)	1.0 (0–5.0)	1.0 (0–4.0)	0.0 (-2.0 to 0)	0.043[b]
Sex	0.0 (0–1.0)	0.0 (0–1.0)	0.0 (0 to 0)	0.0 (0–1.0)	0.0 (0–1.0)	0.0 (0 to 0)	0.891[b]
QoL	4.0 (2.0–8.0)	3.0 (1.0–6.0)	-0.5 (-2.0 to 1.0)	4.0 (2.0– 8.0)	3.0 (1.0–6.0)	-1.0 (-2.0 to 0)	0.563[b]
Voiding diary							
Daytime micturition/24 hr	8.8 (7.0–11.0)	8.0 (6.3– 10.0)	-0.3 (-2.0 to 0.5)[d]	8.3 (7.0– 10.3)	8.3 (6.7–9.3)	-0.3 (-1.3 to 1.3)[d]	1.000[c]
Nocturia/24 hr	1.6 (0.7– 2.3)	1.0 (0.7– 2.0)	-0.1 (-0.7 to 0.3)	1.3 (0.7– 2.0)	1.0 (0.7–1.7)	-0.3 (-0.7 to 0.3)	1.000[c]
Micturition/24 hr	10.0 (8.3– 14.0)	9.7 (7.7– 11.7)	-0.7 (-2.3 to 0.7)[d]	10.0 (8.0– 12.3)	9.5 (7.7–10.7)	-0.3 (-2.0 to 0.7)[d]	1.000[c]
Urgency/24 hr	4.7 (0.3– 9.5)	1.7 (0.0– 7.7)	0.0 (-4.0 to 0.3)	2.0 (0.3– 7.3)	0.7 (0–3.7)	-0.3 (-3.0 to 0.2)	0.750[b]
Uroflowmetry parameters							
Qmax (mL/sec)	9.9 (8.3–12.3)	13.8 (9.5–17.8)	3.5 (-0.6 to 8.2)[d]	11.3 (9.6–12.8)	15.9 (10.4–22.1)	3.8 (0.1 to 11.5)[d]	0.435[b]
VV (mL)	181.0 (128.5–262.0)	194.8 (108.7–293.8)	-4.0 (-78.4 to 78.8)	169.0 (129.1–242.8)	183.9 (123.0–280.5)	3.0 (-71.0 to 84.7)	0.602[b]
PVR (mL)	24.0 (2.0–95.0)	4.0 (0– 46.0)	-10.0 (-50.0 to 6.0)[d]	21.5 (8.0–100)	10.0 (0–30.0)	-9.5 (-60.0 to 2.0)[d]	0.787[b]

Values are presented as mean ± standard deviation or median (interquartile range).
AUA-SS, American Urological Association symptom score; BFLUTS, Bristol female lower urinary tract symptoms; QoL, quality of life; Qmax, maximum flow rate; VV, voided volume; PVR, postvoid residual.
[a]t-test; [b]Mann-Whitney test; [c]Mann-Whitney test with Bonferroni's correction; [d]Statistically significant change within group comparison, $P < 0.05$.

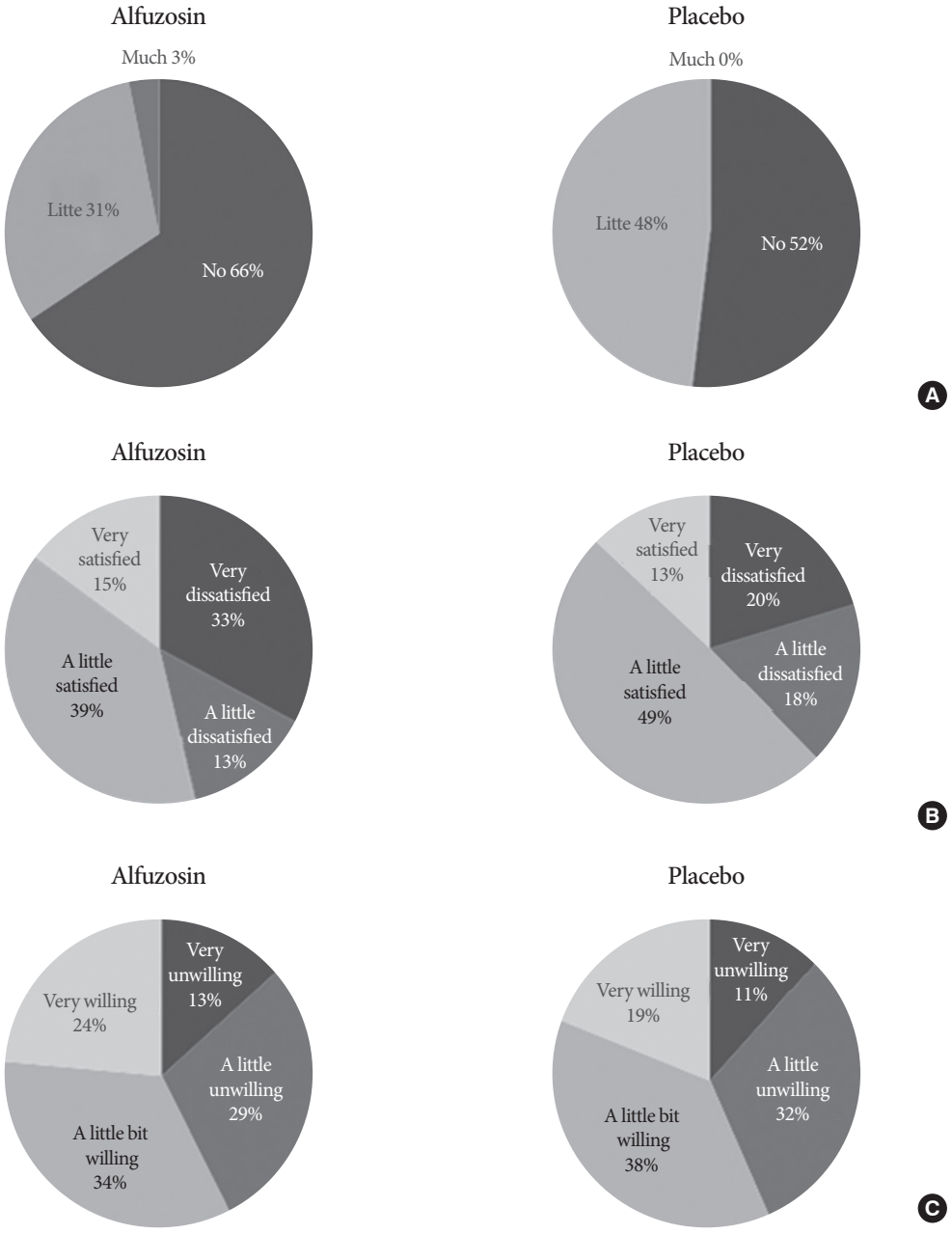

Fig. 3. Differences in treatment benefit, satisfaction, and willingness to continue. (A) Treatment benefit: Mann-Whitney, P = 0.351. (B) Treatment satisfaction: Mann-Whitney, P = 0.726. (C) Willingness to continue: Mann-Whitney, P = 0.792.

voiding diary, and Qmax/PVR were not significantly different between the groups (Table 2). The median changes (interquartile range) in the BFLUTS I-sum were 0.0 (-1.0 to 1.0) in the PLA group and 0.0 (-2.0 to 0) in the ALF group (P = 0.043).

In the context of PPBC, 13% and 55% of the ALF group reported that they had some minor or less than some minor problems at baseline and after treatment, respectively. Similarly, 12% and 61% of PLA patients reported that they had some minor or less than some minor problems at baseline and after treatment, respectively (P = 0.067) (Fig. 2).

Regarding BSW, 34% of the ALF group and 48% of the PLA patients reported that they experienced benefits from treatment

Table 3. Subgroup analysis according to the presence and grade of BOO: between-group comparisons of the changes in efficacy parameters

Parameter	Alfuzosin	Placebo	P-value
Women with BOO	n = 58	n = 59	
AUA-SS			
Total	-7.5 (-13.0 to -4.0)	-7.0 (-12.0 to -2.0)	0.385[a]
Storage	-2.0 (-5.0 to -1.0)	-2.0 (-5.0 to 0)	0.480[a]
Voiding	-4.0 (-9.5 to -2.0)	-5.0 (-8.0 to -2.0)	0.542[a]
Bother score	-1.0 (-2.0 to 0)	-1.0 (-2.0 to 0)	0.628[a]
BFLUTS			
F-sum	-0.5 (-3.0 to 1.0)	-1.0 (-3.0 to 1.0)	0.874[a]
V-sum	-2.2 ± 2.9	-2.0 ± 3.4	0.789[b]
I-sum	0.0 (-1.0 to 2.0)	0.0 (-2.0 to 0)	0.053[a]
Sex	0.0 (0 to 0)	0.0 (0 to 0)	0.753[a]
QoL	0.0 (-2.0 to 1.0)	-0.5 (-2.0 to 1.0)	0.535[a]
Uroflowmetry parameters			
Qmax (mL/sec)	2.3 (-0.8 to 6.3)	4.7 (-0.3 to 11.8)	0.203[a]
VV (mL)	-25.8 (-96.2 to 55.1)	2.3 (-74.1 to 82.8)	0.271[a]
PVR (mL)	-10.0 (-48.5 to 6.5)	-7.5 (-50.0 to 5.5)	0.777[a]
Women with mild BOO	n = 43	n = 47	
AUA-SS			
Total	-8.5 ± 6.1	-7.1 ± 6.8	0.324[b]
Storage	-3.0 ± 3.3	-2.3 ± 2.7	0.319[b]
Voiding	-4.0 (-10.0 to -2.0)	-5.0 (-8.0 to -1.0)	0.483[a]
Bother score	-1.0 (-2.0 to 0)	-1.0 (-2.0 to 0)	0.914[a]
BFLUTS			
F-sum	-1.0 (-3.0 to 1.0)	-1.0 (-3.0 to 1.0)	0.866[a]
V-sum	-2.1 ± 3.0	-1.8 ± 3.6	0.679[b]
I-sum	0.0 (0 to 2.0)	0.0 (-1.0 to 0)	0.073[a]
Sex	0.0 (0 to 0)	0.0 (0 to 0)	0.745[a]
QoL	0.0 (-1.0 to 1.0)	0.0 (-2.0 to 1.0)	0.324[a]
Uroflowmetry parameters			
Qmax (mL/sec)	1.6 (-1.1 to 7.3)	5.0 (0.4 to 12.0)	0.067[a]
VV (mL)	-36.7 (-112.8 to 21.6)	1.6 (-71.3 to 81.0)	0.102[a]
PVR (mL)	0.0 (-30.0 to 9.0)	-6.0 (-50.0 to 2.0)	0.360[a]
Women with moderate-to-severe BOO	n = 15	n = 12	
AUA-SS			
Total	-7.0 (-13.0 to -4.0)	-9.0 (-11.0 to -6.0)	0.677[a]
Storage	-2.9 ± 3.5	-2.6 ± 3.0	0.788[b]
Voiding	-4.0 (-9.0 to -2.0)	-5.0 (-6.5 to -4.0)	0.902[a]
Bother score	-1.0 (-3.0 to 0)	-1.0 (-2.0 to 0)	0.482[a]
BFLUTS			
F-sum	0.0 (-3.0 to 1.0)	-1.0 (-3.0 to 0.5)	0.555[a]
V-sum	-2.5 ± 2.7	-2.9 ± 2.5	0.440[b]
I-sum	0.0 (-2.0 to 0)	-2.5 (-3.0 to 0)	0.112[a]
Sex	0.0 (0 to 0)	0.0 (-1.0 to 0)	0.840[a]
QoL	-1.0 (-3.0 to 1.0)	-1.0 (-2.0 to 0.5)	0.768[a]
Uroflowmetry parameters			
Qmax (mL/sec)	4.6 (1.1 to 5.7)	2.9 (-4.1 to 10.2)	0.366[a]
VV (mL)	49.8 (-48.0 to 63.6)	6.0 (-77.0 to 92.0)	0.460[a]
PVR (mL)	-74.6 ± 97.0	-3.0 ± 70.0	0.051[b]

Values are presented as median (interquartile range) or mean ± standard deviation.
BOO, bladder outlet obstruction; AUA-SS, American Urological Association symptom score; BFLUTS, Bristol female lower urinary tract symptoms; QoL, quality of life; Qmax, maximum flow rate; VV, voided volume; PVR, postvoid residual.
[a]Mann-Whitney test; [b]t-test.

Table 4. Adverse events

Adverse event	Number
Alfuzosin	n = 39
Dizziness	6
GI discomfort	6
Edema	6
Back pain	3
Constipation	3
URI symptoms	3
UTI	3
Residual urine sense	3
Incontinence	2 (stress 1, urge 1)
Palpitation	1
Blurred vision	1
Urethral itching	1
Anxiety	1
Placebo	n = 26
GI discomfort	8
UTI	3
URI	3
Edema	2
Dry mouth	2
Head ache	1
Skin rash	1
Constipation	1
Post-void dribble	1
Febrile sense	1
Leg pain	1
Back pain	1
Urinary hesitency	1

GI, gastrointestinal; URI, upper respiratory tract infection; UTI, urinary tract infection.

(P = 0.351) (Fig 3A). A total of 54% of the ALF patients and 62% of the PLA patients reported that they were satisfied with the treatment (P = 0.726) (Fig. 3B). Finally, 58% of the ALF patients and 57% of the PLA patients wanted to continue the treatment (P = 0.792) (Fig. 3C).

Subgroup Analysis

In the subgroup analysis of women with BOO (58 ALF vs. 59 PLA), changes in the symptom questionnaires (AUA-SS, BFLUTS, and PPBC), voiding diary and Qmax/PVR did not show significant differences between the groups (Table 3). BSW was also not significantly different between the BOO subgroups. In subgroups defined by the grade of BOO, divided into mild (43 ALF vs. 47 PLA) and moderate-to-severe (15 ALF vs. 12 PLA), no significant differences were observed in outcome assessments between the ALF and PLA groups.

Safety Outcomes

Overall, 65 women reported adverse events (AEs) (39 ALF and 26 PLA) (Table 4). In the ALF group, 6 patients reported dizziness and 1 patient discontinued the medication for this reason. No patients in the PLA group reported dizziness. Two patients in the ALF group (1 stomachache, 1 facial edema) and 1 patient in the PLA group (skin rash) discontinued the medication due to AEs. In both groups, most AEs were mild. No severe AEs were reported.

DISCUSSION

Female voiding dysfunction can be caused by urethral and/or detrusor dysfunction. Theoretically, α1-AR blockers improve voiding efficacy by directly increasing urethral relaxation and indirectly reducing the burden on the detrusor muscle. A few clinical trials have showed α1-AR blockers to have a significant effect on female voiding dysfunction [8-10]. However, most of those studies did not have a placebo-controlled design and lacked evidence from a pressure-flow study. Our study was a randomized, double-blind, placebo-controlled trial and included a pressure-flow study to evaluate the efficacy of ALF, an α1-AR blocker, in the treatment of female voiding dysfunction according to the presence or grade of BOO. ALF did not show significant efficacy compared with PLA, although we did not include the target number of subjects. Neither the presence nor the grade of BOO affected the results.

Until now, little clinical data have showed the efficacy of α1-AR blockers for treating female voiding dysfunction. In 1995, Lepor and Theune [17] reported a pilot randomized, double-blind, placebo-controlled trial evaluating the efficacy of terazosin in 29 women with 'prostatism-like symptoms' defined as an AUA-SS ≥ 8. They did not demonstrate the efficacy of terazosin over placebo after 6 weeks of treatment. Two patients (13%) in the placebo group and 7 patients (50%) in the terazosin group prematurely withdrew from the study because of AEs. Given the need for a further study with greater statistical power, Pummangura and Kochakarn [8] conducted a randomized, double-blind, placebo-controlled trial for 140 women with an International Prostate Symptom Score (IPSS) ≥ 8 to evaluate the efficacy of tamsulosin. After 4 weeks of treatment, the mean IPSS change in the tamsulosin group was significantly higher than in the placebo group (-5.6 vs. -2.6). The mean change of Qmax was not significantly different between groups. Low et al. [9] conducted another randomized, double-blind, placebo-con-

trolled trial of terazosin in 100 women with an IPSS ≥8. The primary endpoint was the IPSS quality of life (QoL) index. At the end of 14 weeks of treatment, 80% (32 of 40) of the patients in the terazosin group versus 55% (22 of 40) in the placebo group scored 2 or less on the IPSS QoL index (P<0.02). Moreover, 85% of the terazosin group versus 55% of the placebo group had a total IPSS score of 7 or less (P<0.01).

Although the latter 2 studies might have had sufficient statistical power, they did not include a pressure-flow study, which is the key assessment for evaluating the cause of voiding-phase dysfunction. According to a urodynamic analysis of female voiding dysfunction, approximately 87% of patients had functional BOO and 13% had detrusor underactivity [18]. It is conceivable that a subgroup of women with BOO might respond better to α1-AR blockers than women with detrusor underactivity. We expected that ALF might be more effective in women with BOO than in women without BOO. However, in our study, the results of the pressure-flow study did not demonstrate the efficacy of ALF. Additionally, in our previous observational study, the obstruction grade was not related to the efficacy of tamsulosin, although tamsulosin significantly improved the symptoms of women with voiding dysfunction [10].

Although the idea of using α1-AR blockers in females is not sex-specific, the pathophysiology causing voiding symptoms might have sex-specific mechanisms. For instance, while men with BPO often only have voiding symptoms, many women with voiding symptoms also complain of storage symptoms. Thus, in female patients, physicians should establish whether storage symptoms derive from voiding symptoms or vice versa. Our patients also had storage symptoms (AUA-SS storage score, ALF 9.0 vs. PLA 9.0) and these symptoms may have influenced the voiding symptoms and/or the efficacy of ALF. Considering the effect of storage symptoms in female voiding dysfunction, antimuscarinic treatment prior to or in combination with AR blockers may be efficacious for improving voiding symptoms. Recently, a β-3 agonist has been considered as a treatment option for storage symptoms coexisting with voiding symptoms, because β-3 agonists theoretically do not affect detrusor contractility.

In the study, we chose ALF as the study drug based on the hypothesis that both nonselective and selective AR blockers could antagonize the activity of ARs in the urethra and bladder, thereby improving voiding and storage symptoms. ALF is a non–subtype-selective AR blocker, but it is clinically uroselective and does not significantly affect vascular α-AR receptors. In our study, 6 women complained of dizziness, in the ALF group only. One of these women prematurely dropped out from the study, while the other 5 had mild to tolerable symptoms.

The AUA-SS was evaluated as the primary endpoint. Although the AUA-SS was originally designed to assess the severity of lower urinary tract symptoms in men with BPO, it is now generally accepted as a measure of symptom severity and QoL in women. Grout et al. reported that the AUA-SS might be useful as an indicator to assess bother in women with BOO [19,20].

A limitation of this study is that it was underpowered. Initially, we planned to include 244 women (122 per group). However, recruitment and enrollment were difficult. This may have been because the inclusion criteria were relatively strict (AUA-SS ≥15 and Qmax <15 mL/sec with a voided volume >100 mL and/or a PVR >150 mL) compared to other placebo-controlled studies (AUA-SS ≥8, with no urinary flow criteria) and the requirement for participants to undergo a pressure-flow study. Thus, the negative results of this study should not be interpreted as wholly conclusive.

However, not even a tendency for efficacy was observed. This could mean that there truly is no difference between ALF and PLA, rather than the results being due to an insufficient number of patients. Nonetheless, in the subgroup analysis of women with moderate to severe BOO, the PVR decreased by -74.6±97.0 mL in the ALF group versus -3.0±70.0 mL in the PLA group (Table 3, P=0.051). Because there were only 15 and 12 cases in this subgroup, respectively, if more cases had been included, we may have found ALF to be effective in women with moderate to severe BOO. At the moment, we need to identify the pathophysiological mechanisms that cause voiding dysfunction in women and to prove the efficacy of current treatment options according to these mechanisms through well-designed randomized controlled studies.

In conclusions, a further study with sufficient power, including women with significant BOO, is needed to determine the efficacy of α1-AR blockers for the treatment of female voiding dysfunction. The pathophysiological mechanism should be elucidated. The evaluation and the treatment of female voiding dysfunction should be standardized based on scientific evidence.

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