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Clinical Efficacy and Safety of Naftopidil Treatment for Patients with Benign Prostatic Hyperplasia and Hypertension: A Prospective, Open-Label Study

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Purpose: To investigate the efficacy and safety of naftopidil for benign prostatic hyperplasia (BPH) patients, mainly focusing on changes in blood pressure (BP).

Materials and Methods: Of a total of 118 patients, 90 normotensive (NT) and 28 hypertensive (HT) patients were randomly assigned to be treated with naftopidil 50 mg or 75 mg for 12 weeks, once-daily. Safety and efficacy were assessed by analyzing changes from baseline in systolic/diastolic BP and total International Prostate Symptom Score (IPSS) at 4 and 12 weeks. Adverse events (AEs), obstructive/irritative subscores, quality of life (QoL) score, maximum urinary flow rate (Qmax), and benefit, satisfaction with treatment, and willingness to continue treatment (BSW) questionnaire were also analyzed.

Results: Naftopidil treatment decreased mean systolic BP by 18.7 mm Hg for the HT 50 mg group (p<0.001) and by 18.3 mm Hg for the HT 75 mg group (p<0.001) and mean diastolic BP by 17.5 mm Hg for the HT 50 mg group (p<0.001) and by 14.7 mm Hg for the HT 75 mg group (p=0.022). In the NT groups (both naftopidil 50 mg and 75 mg), naftopidil elicited no significant changes in BP from baseline values. After 12 weeks, naftopidil 50 and 75 mg groups showed significant improvements in IPSS scores (total, obstructive/irritative subscores, QoL score) and Qmax from baseline. AEs were reported in 7.8% (50 mg group) and 2.9% (75 mg group) of patients. In both the 50 mg and 75 mg groups, >86% of all patients agreed to continue their current medications.

Conclusion: Our results suggest that naftopidil treatment in BPH patients with hypertension allows for optimal management of BP within the normal range.

Key Words: α-adrenoceptor antagonists, BPH, hypertension, naftopidil

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common urological disorder in older men, and its incidence is expected to rise with increasing life expectancy. Hypertension is also a common disease in older age adults. Studies suggest that age-related increases in sympathetic noradrenergic activity may be a common pathophysiologic component in BPH and hypertension.[1-4] Even disregarding the possibility of a common pathology, it is estimated that at least one in four men aged >60 years could have concomitant BPH and hypertension.[4,5]

Selective α1-adrenoceptor (AR) antagonists are well known to be an effective, non-invasive treatment option for patients with BPH. Lower urinary tract symptoms (LUTS) can be improved by reduction of urethral pressure and prostatic smooth muscle tone by blocking the motor sympathetic adrenergic nerve supply to the prostrate. These agents are currently considered as first-line medical therapy for BPH patients,[5-7] and numerous studies regarding their efficacy and tolerability have been reported.

Of these agents, naftopidil is an α1-AR antagonist that has high selectivity for the α1D subtype, showing 3- and 17-fold higher

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affinity for this subtype than for α1A and α1B subtypes, respectively.[8,9] Although several clinical trials[9-12] demonstrating the efficacy of this drug for BPH patients have been reported, there are few reports of the cardiovascular responses associated with this drug during BPH treatment. Here, we aimed to determine the efficacy and safety of naftopidil for BPH/LUTS patients, focusing on 1) changes in blood pressure (BP) and 2) patient satisfaction and compliance.

MATERIALS AND METHODS

Study design

This study was designed as a prospective, open-label study to determine the efficacy and safety of naftopidil (Flivas, Dong-A Pharmaceutical Co., Ltd., Seoul, Korea) at a single center (Yonsei University Health System, Severance Hospital, Seoul, Korea). The study protocol was approved by our Institutional Review Board (IRB approval No. 4-2014-0503, Yonsei University Health System). Patients provided written consent to participate in the study after having received an explanation of the protocol, including awareness of possible side effects.

Based on an assumption of a mean improvement in total international prostate symptom score (IPSS) from baseline of 3.0, a standard deviation of 5.3, and the assumption that 20% of patients will not be valid for inclusion in the per-protocol population, a sample size of at least 120 patients was required to obtain a power of 90%, with type 1 error of 0.05 (for a two-sided test). Results are reported for the intention to treat (ITT) population (all patients with a baseline BP and IPSS assessment and at least one valid post-baseline BP and IPSS assessment).

The enrolled patients suffered from LUTS and were considered fit for α1-AR antagonist treatment based on the decision of our physician. Patients who met the inclusion criteria were assigned into the normotensive (NT) group (defined as diastolic BP <90 mm Hg in a sitting position) or hypertensive (HT) group (diastolic BP ≥90 mm Hg in a sitting position) and then randomly assigned by computer-generated random numbers into the naftopidil 50 mg group or 75 mg group for 12-week, once-daily treatment.

BP was measured according to previous published guidelines:[13,14] 1) patients were seated quietly for at least 5 minutes in a chair with their feet on the floor and arms at the level of the heart, 2) at least two measurements at 1–2 minute intervals were made, 3) we used a standard bladder (12–13×35 cm), a larger one for big arms, and 4) we deflated the cuff slowly (2 mm Hg/sec). Patient visits occurred at study entry and after 4 weeks and 12 weeks of treatment. Adverse events (AEs) were defined as symptoms that required discontinuation or change of the current medication.

Study population

The inclusion criteria included male ambulatory patients over 50 years of age with LUTS (total IPSS greater than 8). Patients with the following conditions were excluded: allergic drug reaction to α1-AR antagonists, orthostatic hypotension, a history of prostate-related surgery (open or endoscopic), suspicious prostate malignant condition on digital rectal examination and/or prostate-specific antigen (PSA) >10 ng/mL, a history of recurrent urinary tract infection or bladder stones, renal impairment (creatinine clearance rate <30 mL/min), severe hepatic disorders, the use of anticholinergic or cholinergic agents, the use of other α1-AR antagonists (tamsulosin, silodosin, alfuzosin, doxazocin, terazocin) within the previous 4 weeks, or the use of 5-reductase inhibitors or antiandrogens within the previous 3 months. Patients who were currently receiving or were planning to take any α-receptor agonists or β-receptor antagonists were also excluded.

Study end-points and assessments

The primary end-point of this study was to determine the safety and efficacy of naftopidil 50 and 75 mg treatment. This measure was assessed by analyzing changes from baseline in systolic/diastolic BP and total IPSS at 4 and 12 weeks. Secondary aims were to analyze 1) AEs; 2) improvement in IPSS obstructive/irritative subscores, IPSS quality of life (QoL) score, and maximum urinary flow rate (Qmax); and 3) benefit, satisfaction with treatment, and willingness to continue treatment (BSW) questionnaire with naftopidil 50 and 75 mg treatment at 4 and 12 weeks. The safety population was all patients who were randomized and who received at least one dose of study medication.

Statistical analysis

The two-sample t-test and Wilcoxon rank sum test were conducted to analyze continuous variables, and the chi-square test was used to analyze categorical variables. Comparison of the efficacy variables was performed using an RM-ANOVA model with baseline values of the response variable as covariates for absolute change in IPSS from baseline. For efficacy evaluations, the last observation carried forward was applied to analyze the ITT population. Statistical analysis was performed with Prism software (version 5.00; GraphPad Instat, San Diego, CA, USA). Results were considered significant at $p<0.05$.

RESULTS

Study design

A total of 120 patients were screened and 118 were enrolled in this study (Fig. 1). Of these, 90 NT patients and 28 HT patients were randomized to receive naftopidil 50 mg or naftopidil 75 mg (group 1, NT 50 mg naftopidil; group 2, NT 75 mg naftopidil; group 3, HT 50 mg naftopidil, group 4, HT 75 mg naftopidil). In the NT group, 83 patients completed the study. The main reason for study discontinuation was AEs (6 patients, 6.6%), and one patient withdrew informed consent. In the HT group,

27 patients completed the study, and one discontinued because of loss during follow-up.

Patient demographics and characteristics

Baseline demographics and characteristics for all patients in the ITT population are shown in Table 1. There were no significant

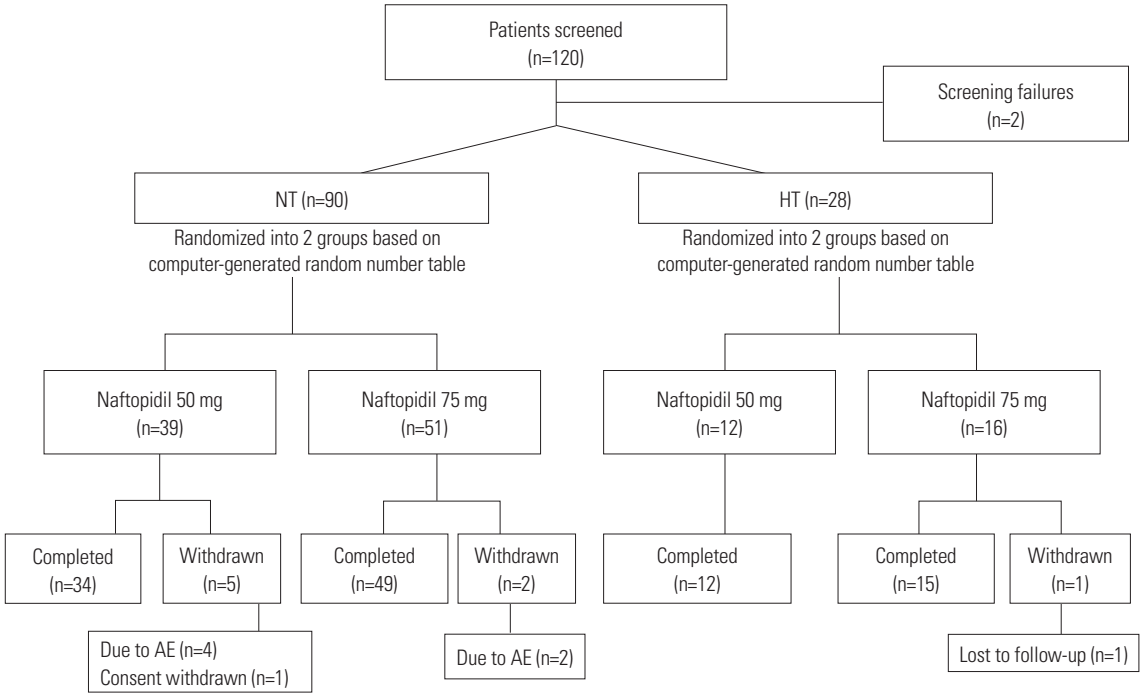

Fig. 1. Patient disposition. A total of 120 patients were screened and 118 were enrolled in this study. Ninety normotensive (NT) patients and 28 hypertensive (HT) patients were randomly assigned into the naftopidil 50 mg or naftopidil 75 mg group for 12-week, once-daily treatment. In the NT group, 83 patients completed the study. The main reason for study discontinuation was AEs (6 patients, 6.6%). In the HT group, 27 patients completed the study, and one discontinued because of loss during follow-up. AE, adverse event.

Table 1. Patient Demographics and Baseline Characteristics

	Normotension		Hypertension		*p* value
	Group 1 (naftopidil 50 mg)	Group 2 (naftopidil 75 mg)	Group 3 (naftopidil 50 mg)	Group 4 (naftopidil 75 mg)	
No. of patients	39	51	12	16	-
Mean (SD)					
Age, yr	65.5 (7.0)	67.2 (6.5)	62.2 (4.3)	64.1 (7.4)	0.151
Height, cm	168.4 (4.2)	166.9 (7.2)	168.4 (4.2)	170.7 (6.3)	0.382
Weight, kg	65.6 (7.0)	67.8 (11)	69.2 (6.9)	70.5 (10.2)	0.548
SBP, mm Hg	123.1 (10.1)	124.9 (12.4)	144.4 (21.0)	145.3 (6.6)	<0.001
DBP, mmHg	78.1 (6.5)	77.1 (9.7)	4.0 (3.0)	93.5 (2.8)	<0.001
Prostate volume, mL	30.4 (9.9)	31.9 (8.4)	7.5 (7.3)	35.0 (10.6)	0.394
PSA, ng/mL	1.5 (1.1)	1.9 (2.2)	1.3 (1.3)	1.9 (1.7)	0.703
IPSS (baseline)					
Total	18.8 (5.2)	19.8 (6.5)	17.4 (5.6)	17.5 (3.1)	0.595
Obstructive subscore	13.3 (4.3)	13.5 (5.1)	12.1 (4.2)	12.2 (3.9)	0.822
Irritative subscore	5.3 (2.2)	6.3 (2.7)	5.2 (3.0)	5.3 (1.9)	0.425
QoL score	4.1 (0.7)	4.5 (0.7)	4.0 (0.8)	4.2 (0.8)	0.169
Qmax, mL/sec	11.7 (2.8)	10.8 (2.7)	11.6 (3.3)	9.6 (3.0)	0.260
PVR, mL	26.1 (27.5)	30.7 (38.3)	20.0 (19.7)	44.2 (55.6)	0.532
Race (%)					
Asian	100	100	100	100	-

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; PSA, prostate specific antigen; IPSS, international prostate symptom score; QoL, quality of life; Qmax, maximum urinary flow rate; PVR, post-void residual urine volume.

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differences between the four treatment groups in regards to age, height, weight, prostate volume, level of PSA, total IPSS scores, IPSS obstructive or irritative subscore, QoL due to urinary symptoms, Qmax, or post-void residual urine volume. Systolic and diastolic BP were significantly different between groups 1 and 2 and groups 3 and 4 (p<0.001).

Influence on BP

Naftopidil treatment decreased the mean systolic BP by 18.7 mm Hg for group 3 (p<0.001) and by 18.3 mm Hg for group 4 (p<0.001) and the mean diastolic BP by 17.5 mm Hg for group 3 (p<0.001) and by 14.7 mm Hg for group 4 (p=0.022) (Fig. 2). However, in the NT groups (both naftopidil 50 and 75 mg), naftopidil caused no significant changes in BP from baseline values. After adjusting for age, significant changes in mean systolic and diastolic BPs from baseline values were found in group 3 and group 4 vs. group 1 and group 2 (Fig. 2).

Efficacy

The efficacy of naftopidil 50 and 75 mg on LUTS is summarized in Fig. 3. After 12 weeks of treatment, both groups showed significant improvements from baseline in total IPSS score (p<0.001). For both obstructive and irritative subscores, there were significant improvements from baseline to the final visit for both 50 and 75 mg doses (p<0.001 and p=0.028, respectively). Also, IPSS QoL scores after treatment with both drug doses improved significantly at 12 weeks (p<0.001). Both groups showed significant improvement in Qmax from baseline at 12 weeks (p=0.034 in naftopidil 50 mg group and p<0.001 in 75 mg group).

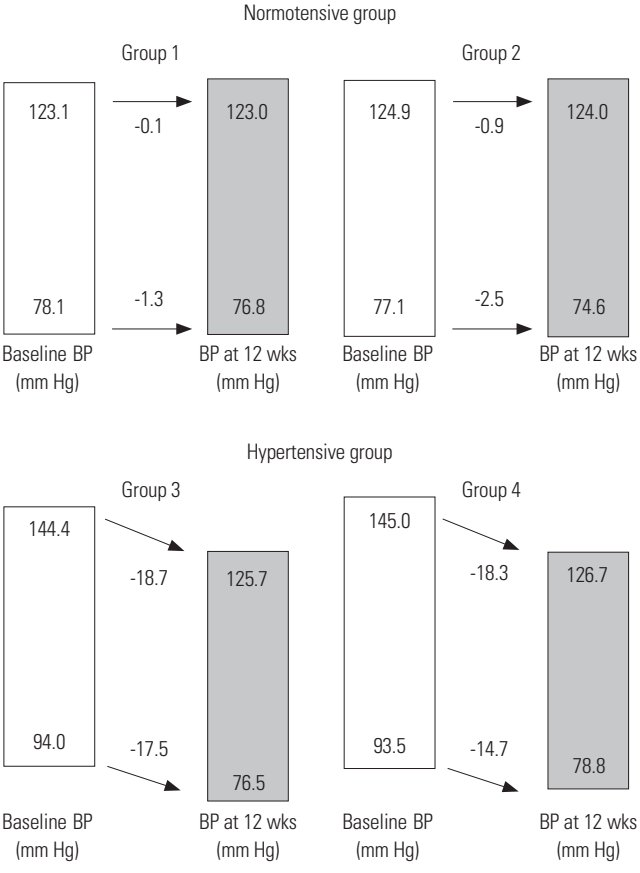

Fig. 2. Comparison of the mean changes in BP from baseline value according to group. BP, blood pressure.

Safety

AEs were reported in four of 51 patients (7.8%) receiving naftopidil 50 mg and in two of 67 (2.9%) receiving naftopidil 75 mg (Table 2). No syncope was reported for either group. None of the patients reported retrograde ejaculation. Most AEs were mild or moderate in severity.

Satisfaction and compliance

After completion of 12 weeks of treatment with naftopidil, satisfaction and compliance with this drug were assessed using the BSW questionnaire (Table 3). In both the 50 and 75 mg group, >76.6% of all patients felt they benefited from the treatment and were satisfied therewith. Moreover, 95.7% of patients in the naftopidil 50 mg group and 86% in the 75 mg group agreed to continue their current medications. The reasons for discontinuation were gastrointestinal trouble (n=2 in naftopidil 50 mg group and n=5 in 75 mg group) and dizziness (n=4 in naftopidil 75 mg group).

DISCUSSION

Considering the high incidence of patients with concomitant BPH and hypertension, physicians are concerned about the influence of BP changes during α1-AR antagonist treatment in such cases. Many studies regarding BP change in patients with BPH/hypertension treated with α1-AR antagonist have been reported. In 1995, Kirby[15] reported that 12 weeks of treatment with doxazosin resulted in significant reductions in BP in HT patients, whereas minimal reductions were found in placebo-treated patients. Kaplan, et al.[16] showed that doxazosin treatment did not cause a clinically significant BP change in NT patients. Chung and Hong[5] reported that doxazosin gastrointestinal therapeutic system (GITS) treatment for 1 year resulted in a significantly greater reduction in BP in HT patients, compared with NT patients. Lee, et al.[3] compared the BP-lowering effect of α1-AR antagonists in patients with or without concomitant antihypertensive drug treatment and reported that doxazosin GITS treatment resulted in optimal management of BP within the normal range, especially in baseline HT BP patients, irrespective of concomitant antihypertensive medication. Fawzy, et al.[4] demonstrated that doxazosin is especially beneficial in the treatment of concomitant BPH and hypertension. Considering that older men might already be taking multiple medications for other diseases, the use of a single drug for two diseases might be valuable.

The majority of these reports, however, concern doxazosin treatment. Because doxazosin is a non-uroselective α1-AR antagonist, its influence on BP might be understandable. However, there are few reports on BP change with naftopidil, an α1-AR antagonist that has a high affinity for the α1D subtype. In our institution, we experienced stabilization of BP during naftopidil treatment for BPH/LUTS. From our experience, we think that this additional benefit of BPH medication results in increased satisfaction and compliance of the patients with this drug. Therefore, we aimed to further investigate the influence of naftopidil, mainly focusing on the cardiovascular aspects (i.e., BP change), as well as its efficacy for LUTS and patient satisfaction/compliance.

In terms of BP change with uroselective α1-AR antagonist in HT patients, a previous report[3] showed that treatment with tamsulosin and alfuzosin resulted in only a slight reduction in systolic BP. However, in the present study, treatment with naftopidil 50 mg or 75 mg resulted in significant reductions in sys-

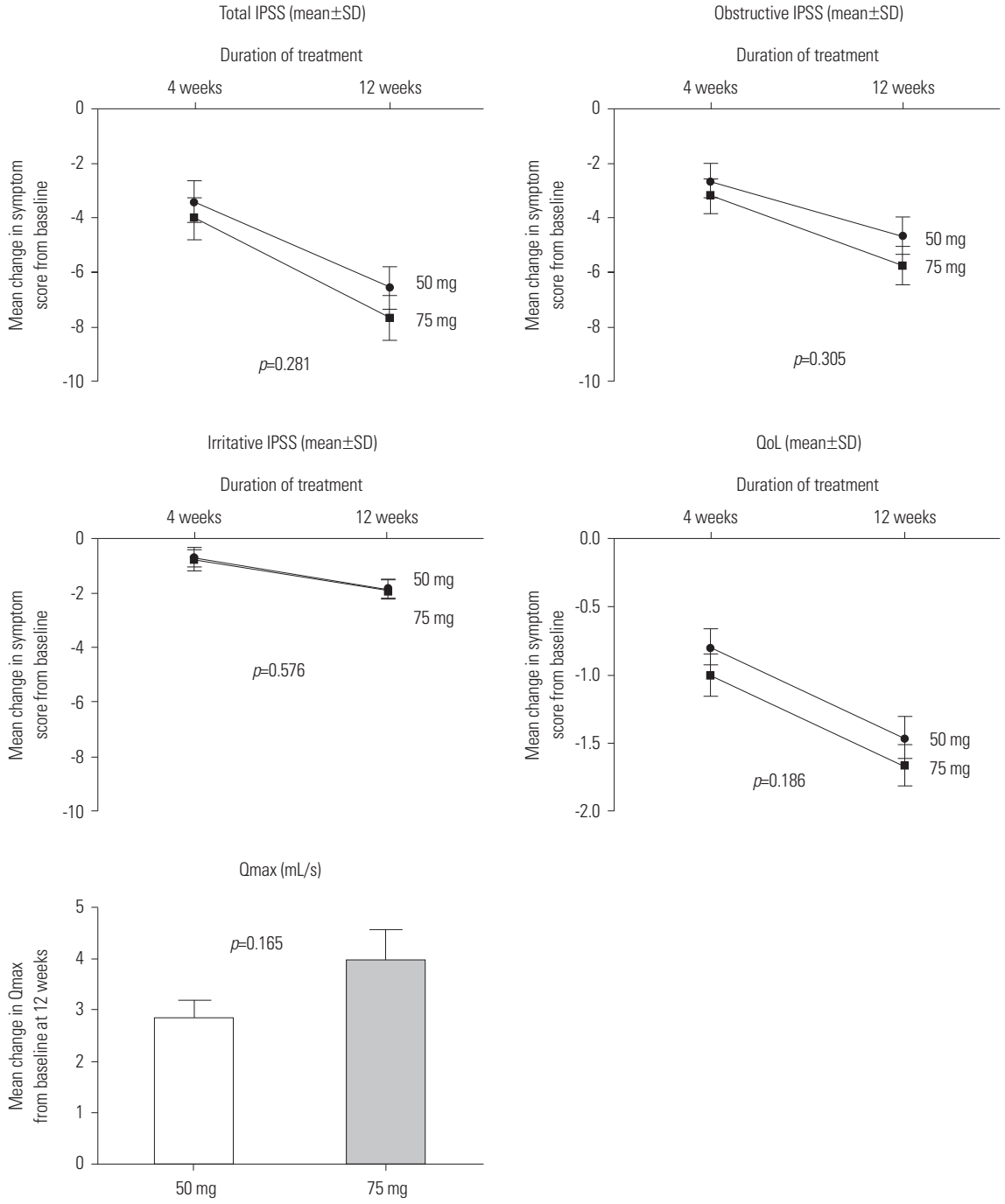

Fig. 3. Change in efficacy parameters from baseline to each visit in the ITT population. IPSS, international prostate symptom score; SD, standard deviation; QoL, quality of life; Qmax, maximum urinary flow rate; ITT, intention to treat.

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Table 2. Summary of Adverse Events*

	Naftopidil 50 mg (n=51)	Naftopidil 75 mg (n=67)
Dizziness, n (%)	2 (3.9)	1 (1.4)
Orthostatic hypotension, n (%)	0 (0)	0 (0)
Syncope, n (%)	0 (0)	0 (0)
Headache, n (%)	0 (0)	0 (0)
Retrograde ejaculation, n (%)	0 (0)	0 (0)
Insomnia, n (%)	0 (0)	0 (0)
Chest pain, n (%)	0 (0)	0 (0)
Asthenia, n (%)	0 (0)	0 (0)
Flu-like symptom, n (%)	0 (0)	0 (0)
GI trouble, n (%)	2 (3.9)	1 (1.4)

*The safety population comprised all subjects who were randomized and received at least one dose of the study medication.

Table 3. Results of the BSW Questionnaire

	Naftopidil 50 mg group (n=46)	Naftopidil 75 mg group (n=64)
Subscales, n (%)		
Patient perception of treatment benefit (BSW-1)		
No benefit	7 (15.2)	14 (21.9)
Little benefit	0 (0)	0 (0)
Much benefit	39 (84.8)	50 (78.1)
Patient satisfaction with treatment (BSW-2)		
Dissatisfied	6 (13.0)	15 (23.4)
Satisfied	40 (87.0)	49 (76.6)
Patient willingness to continue with treatment (BSW-3)		
Unwilling	2 (4.3)	9 (14.0)
Willing	44 (95.7)	55 (86.0)

BSW, benefit, satisfaction with treatment, and willingness to continue treatment.

tolic and diastolic BP in baseline HT patients (Fig. 2). In NT patients, systolic and diastolic BP were optimally managed with naftopidil.

The pharmacological mechanism of the BP-lowering effect associated with naftopidil could be related to calcium-channel-blocking activity. In 1991, Himmel, et al.[17] reported that naftopidil could act as a weak ligand for L-type calcium channels, leading to ca^{2+} antagonistic effects. Similarly, several reports[18,19] demonstrated that naftopidil has both α-AR and calcium-blocking activity. We think further studies are needed to address this.

In the present study, results from the BSW questionnaire suggested that treatment with naftopidil also shows increased satisfaction and compliance with this drug among patients. In both the 50 and 75 mg groups, the majority of patients felt benefit with satisfaction and agreed to continue this drug (Table 3).

Analysis of the BP-lowering effect of naftopidil with or without concomitant antihypertensive medication revealed significant reductions in systolic and diastolic BP in baseline HT patients, irrespective of concomitant antihypertensive medication (data not shown). These results are consistent with the previous report by Lee, et al.[3] Regarding efficacy, the overall efficacy of BPH treatment with naftopidil for 12 weeks in the present study was similar to the results of a previous study.[9] When comparing naftopidil 50 mg vs. 75 mg groups, overall efficacy parameters were superior with the higher dose (75 mg), although the differences were not statistically significant (Fig. 3). In addition, several studies[10,20-23] on naftopidil treatment reported improvement of irritative symptoms with this drug. Nishino, et al.[10] reported that naftopidil was better than tamsulosin for nocturia. Other series[24-26] suggested that upregulation of α1D-AR in the bladder contributes to the storage symptoms observed in bladder outlet obstruction and that targeting the α1D-AR with naftopidil may provide a new therapeutic approach for controlling storage symptoms in patients with BPH. However, in our study, we noted little difference in improvement in storage symptoms, compared with other α1-AR antagonists.

There are several limitation in our study. First, the study included a relatively small number of patients and a short period of follow-up. Second, we measured BP only with the patient in the seated position. We acknowledge the methodological flaw of not measuring BP in a supine position, in addition to the sitting position, to rule out any orthostatic hypotension that might be present. Finally, we were unable to determine why the naftopidil treatment lowered BP in HT patients, compared with NT patients, and future studies to elucidate the underlying mechanism will be needed. However, we think that our results provide adequate preliminary data to support the additional benefit (optimal management of BP within the normal range) of naftopidil treatment in BPH/LUTS patients.

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