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Original Article

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A Randomized Study Comparing Once-Daily and Thrice-Daily Naftopidil 75 mg/Day for Lower Urinary Tract Symptoms of Benign Prostatic Hyperplasia

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Abstract

Background: The efficacy and tolerability of naftopidil 75 mg administered once daily (OD) in the evening (group O) were compared to those of naftopidil 25 mg thrice daily (TID), given in the morning, afternoon and evening (group T), for lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH). The factors predicting the efficacy of each dosage regimen were also examined.

Methods: The participants were 101 patients with LUTS/BPH who were randomly administered naftopidil for 8 weeks in either group O or group T. Inclusion criteria were international prostate symptom score (IPSS) ≥ 8 and IPSS quality of life (IPSS-QoL) ≥ 3.

Results: IPSS total score, IPSS-QoL and the BPH impact index were all significantly improved compared to baseline for both groups at 8 weeks after treatment. Voided volume, maximum flow rate and average flow rate were significantly improved compared to baseline only for group O at 8 weeks after treatment. The effectiveness rate based on the criteria for treatment efficacy of the Japanese clinical practice guideline for voiding dysfunction was not significantly different between the two groups. There was no independent predictive factor for the efficacy of naftopidil in group O, but prostate volume and symptom severity were identified as predictive factors in group T. The rate of adverse events was not significantly different between the two groups.

Conclusions: The overall efficacy of naftopidil 75 mg/day given OD was approximately equal to that of 75 mg/day TID, but OD therapy was objectively more effective. LUTS/BPH patients with large prostate volume should be given OD therapy because the therapy is not affected by the severity of subjective symptoms or prostate volume.

Keywords: Benign prostatic hyperplasia; Dosage method; Naftopidil; Predictive factor

Introduction

Benign prostatic hyperplasia (BPH) decreases quality of life (QoL) because of lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO).

Naftopidil has higher selectivity for the lower urinary tract, because it is an α1D/A-adrenoceptor (α1D/A-AR) antagonist that has higher affinity for the α1D-adrenoceptor (α1D-AR) subtype. Therefore, it shows fewer adverse effects related to blood pressure [1]. The effects of naftopidil are dose-dependent, and the optimal dosage for the treatment of LUTS associated with BPH (LUTS/BPH) in Japan is recommended to be from 25 mg/day to 75 mg/day [2].

Recently, the dosage regimen of the drug has been changed to once daily (OD) to improve compliance. Similarly, the tolerability of naftopidil 75 mg given OD has been reported [3, 4]. However, combination therapy with a drug given OD and drugs given twice (or more than twice) in divided doses is complicated for patients who already take drugs in divided doses. It has been reported that a decrease in the number of combination drugs and changing to a simple dosage regimen improves compliance [5]. Since a complicated dosage regimen affects compliance, it is necessary to consider the most suitable dosage regimen for each patient. In addition, cases of patients in whom a thrice-daily (TID) regimen of naftopidil had to be considered because the patients were taking other drugs on a TID basis also arose. However, the kind of patient who would have a good response with each regimen (OD and TID) has not been considered.

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Table 1. Baseline Characteristics of the Two Groups

	Total (n)	Group O (n)	Group T (n)	Intergroup P value
Age (years)	69.4 ± 8.2 (101)	68.5 ± 8.3 (51)	70.4 ± 8.0 (50)	NS[a]
Prostate volume (mL)	26.0 ± 13.8 (98)	27.3 ± 14.7 (50)	24.7 ± 12.9 (48)	NS[a]
IPSS total score	15.5 ± 6.0 (101)	14.7 ± 5.2 (51)	16.3 ± 6.7 (50)	NS[b]
IPSS-QoL	4.5 ± 0.9 (101)	4.5 ± 0.9 (51)	4.4 ± 1.0 (50)	NS[b]
BPH impact index	5.1 ± 2.7 (100)	5.1 ± 2.7 (50)	5.1 ± 2.8 (50)	NS[b]
Voided volume (mL)	170.4 ± 116.3 (70)	159.5 ± 115.7 (35)	181.2 ± 117.5 (35)	NS[b]
Max flow rate (mL/s)	10.6 ± 6.0 (70)	10.3 ± 5.7 (35)	10.9 ± 6.3 (35)	NS[b]
Average flow rate (mL/s)	5.8 ± 3.2 (69)	5.8 ± 3.3 (34)	5.7 ± 3.1 (35)	NS[b]
Post void residual urine (mL)	66.4 ± 77.2 (70)	70.1 ± 85.7 (34)	62.9 ± 69.3 (36)	NS[b]

Mean ± SD. [a]Unpaired *t*-test; [b]Mann-Whitney U test.

The present study compared the efficacy and tolerability of naftopidil given as 75 mg/day OD and given as 75 mg/day TID for LUTS/BPH and investigated the predictive factors for efficacy of each dosage regimen.

Materials and Methods

The participants in this study were 101 patients who had been clinically diagnosed with LUTS/BPH in the Department of Urology at Kurobe City Hospital and Saiseikai Toyama Hospital between September 2005 and April 2009.

The inclusion criteria were international prostate symptom score (IPSS) ≥ 8 and IPSS-QoL ≥ 3. The exclusion criteria included presence of urinary retention, post-void residual urine volume (PVR) ≥ 200 mL, hydronephrosis and/or renal impairment caused by BOO, intractable hematuria, prostate cancer, history of prostatic surgery, neurogenic bladder, urethral stricture, or chronic bacterial prostatitis. The enrolled patients were randomly divided into two groups based on medical chart numbers after their informed consent was obtained, and characteristics such as age, complications and estimated prostate volume (PV) by transabdominal ultrasonography (TRUS) were investigated. Naftopidil 75 mg/day OD in the evening was administered to the 51 odd-numbered patients (group O), while naftopidil 75 mg/day TID (25 mg once in the morning, afternoon and evening) was administered to the 50 even-numbered patients (group T) for 8 weeks.

At baseline and 8 weeks after treatment, subjective symptoms and objective findings were assessed using the IPSS, IPSS-QoL, BPH impact index (BII), voided volume (VV), maximum flow rate (MFR), average flow rate (AFR) and PVR as measured by TRUS. In addition, overall severity and treatment efficacy using the criteria for treatment efficacy in BPH proposed by the Japanese Urological Association in 1997 [6] were evaluated. All study protocols were approved by the Institutional Review Board for Clinical Study at Saiseikai Toyama Hospital.

Statistical analysis

Results are expressed as means ± standard deviation (SD). Paired t-tests were used to compare blood pressures between baseline and 8 weeks. Unpaired t-tests were used to compare age, estimated PV and blood pressure between groups. For all other parameters, the Wilcoxon signed-rank test was used for comparisons between baseline and 8 weeks, while the Mann-Whitney U test was used for comparisons between groups. The effectiveness rate using the criteria for treatment efficacy in BPH proposed by the Japanese Urological Association and adverse events were compared used the Chi-square test. Logistic regression analysis was used to identify predictive factors for the efficacy of each dosage method. Values of $P < 0.05$ were considered significant.

Results

The characteristics of the 101 patients enrolled in this study (group O, n = 51; group T, n = 50) are shown in Table 1. No significant differences were apparent between the groups. Adverse events were evaluated in these 101 patients. Among the 101 patients, four (group O, n = 2; group T, n = 2) with IPSS < 8, three (group O, n = 2; group T, n = 1) with IPSS-QoL < 3, three (group O, n = 1; group T, n = 2) for whom baseline PV was not measured and one patient (group O, n = 1) for whom baseline BII was not measured were excluded. Efficacy was thus evaluated in 90 patients and compared between 45 patients in group O and 45 patients in group T.

Overall severity using the criteria for treatment efficacy in BPH proposed by the Japanese Urological Association is shown in Table 2. These parameters showed no significant differences between groups O and T.

Differences in IPSS total score, IPSS-QoL and BII total score are shown in Table 3. All parameters were significantly improved at 8 weeks compared with baseline in groups O and T. The changes of these parameters at 8 weeks compared to baseline showed no significant differences between groups O and T.

Differences in objective findings are shown in Table 4. VV, MFR and AFR were significantly improved at 8 weeks compared with baseline in group O, but not significantly improved in group T. The changes of these parameters at 8 weeks compared to baseline showed no significant differences between groups O and T.

Treatment efficacy using the criteria for treatment efficacy in BPH proposed by the Japanese Urological Association is shown in Table 5. The patients judged to be "excellent", "good" and "fair" were defined as effective cases, and the patients judged to be "poor/worse" were defined as insufficient effect cases. The efficacy rates are shown in Table 5. The efficacy rates for symptoms, QoL and function were 62.2%/62.2%, 88.9%/80.0% and 45.5%/42.4%, respectively (group O/group T). The overall efficacy rate was 67.6% in group O and 64.1% in group T. These parameters showed no significant differences between groups O and T.

Logistic regression analysis was used to identify predictive factors for efficacy with each dosage method. The dependent variable was the effective and insufficient effect cases, and the independent variables were age, PV, symptom severity, severity of QoL, severity of dysfunction and BII at baseline. The results are shown in Table 6. No factor related to efficacy was identified in group O, while PV (odds ratio: 1.13) and symptom severity (odds ratio: 0.06) were identified in group T.

An adverse event was encountered in only one patient in group O (dryness of the mouth, 2.0%), and no significant

Table 2. Overall Severity

Criteria for overall severity	Group	Mild		Moderate		Severe		Intergroup P value
		n	(%)	n	(%)	n	(%)	
Symptom (IPSS)	Group O	0	(0.0)	36	(80.0)	9	(20.0)	NS
	Group T	0	(0.0)	32	(71.1)	13	(28.9)	
QoL (IPSS-QoL)	Group O	0	(0.0)	22	(48.9)	23	(51.1)	NS
	Group T	0	(0.0)	25	(55.6)	20	(44.4)	
Function (Qmax)	Group O	9	(20.9)	30	(69.8)	4	(9.3)	NS
	Group T	9	(20.9)	31	(72.1)	3	(7.0)	
Overall severity	Group O	1	(2.2)	36	(80.0)	8	(17.8)	NS
	Group T	2	(4.7)	31	(72.1)	10	(23.3)	

Overall severity was evaluated by the criteria for treatment efficacy in BPH proposed by the Japanese Urological Association. Chi-square test.

Table 3. Differences in IPSS, IPSS-QoL and BII

	Group	N	Baseline	8 weeks	Intragroup P value	Difference
IPSS total score	Group O	45	15.0 ± 5.2	9.7 ± 5.0	< 0.001	-5.3 ± 4.7
	Group T	45	16.8 ± 6.4	11.3 ± 5.0	< 0.001	-5.5 ± 5.6
	Intergroup P value		NS	NS		NS
IPSS-QoL	Group O	45	4.6 ± 0.7	2.9 ± 1.0	< 0.001	-1.8 ± 1.2
	Group T	45	4.5 ± 0.8	3.1 ± 1.2	< 0.001	-1.5 ± 1.2
	Intergroup P value		NS	NS		NS
BII total score	Group O	45	5.3 ± 2.7	2.7 ± 2.1	< 0.001	-2.6 ± 2.0
	Group T	45	5.4 ± 2.6	3.2 ± 2.3	< 0.001	-2.2 ± 2.8
	Intergroup P value		NS	NS		NS

Mean ± SD (range). Intragroup: Wilcoxon signed-rank test; intergroup: Mann-Whitney U test.

Table 4. Differences in Objective Findings

	Group	N	Baseline	8 weeks	Intragroup P value	Difference
Voided volume (mL)	Group O	33	162.8 ± 118.3	209.4 ± 142.5	0.017	46.6 ± 105.6
	Group T	33	184.8 ± 119.3	196.7 ± 109.4	NS	11.8 ± 151.6
	Intergroup P value		NS	NS		NS
Max flow rate (mL/s)	Group O	33	10.4 ± 5.8	13.0 ± 6.1	0.003	2.5 ± 4.9
	Group T	33	10.8 ± 6.3	12.3 ± 6.1	NS	1.5 ± 6.0
	Intergroup P value		NS	NS		NS
Average flow rate (mL/s)	Group O	32	5.8 ± 3.4	7.6 ± 4.1	0.003	1.8 ± 3.0
	Group T	33	5.7 ± 3.0	6.5 ± 3.7	NS	0.8 ± 2.8
	Intergroup P value		NS	NS		NS
Post void residual urine (mL)	Group O	32	60.2 ± 78.0	54.5 ± 91.0	NS	-5.7 ± 52.3
	Group T	34	66.2 ± 69.9	38.2 ± 43.2	NS	-28.0 ± 66.9
	Intergroup P value		NS	NS		NS

Mean ± SD (range). Intragroup: Wilcoxon signed-rank test; intergroup: Mann-Whitney U test.

Table 5. Criteria for Treatment Efficacy

	Group (n)	Excellent		Good		Fair		Poor		Intergroup P value
		n	(%)	n	(%)	n	(%)	n	(%)	
Symptom (IPSS)	Group O (45)	4	(8.9)	10	(22.2)	14	(31.1)	17	(37.8)	NS
	Group T (45)	1	(2.2)	8	(17.8)	19	(42.2)	17	(37.8)	
QoL (IPSS-QoL)	Group O (45)	4	(8.9)	7	(15.6)	29	(64.4)	5	(11.1)	NS
	Group T (45)	1	(2.2)	7	(15.6)	28	(62.2)	9	(20.0)	
Function (Qmax)	Group O (33)	0	(0.0)	10	(30.3)	5	(15.2)	18	(54.5)	NS
	Group T (33)	1	(3.0)	9	(27.3)	4	(12.1)	19	(57.6)	
Overall efficacy	Group O (37)	1	(2.7)	8	(21.6)	16	(43.2)	12	(32.4)	NS
	Group T (39)	0	(0.0)	5	(12.8)	20	(51.3)	14	(35.9)	

Treatment efficacy was evaluated by the criteria for treatment efficacy in BPH proposed by the Japanese Urological Association. Overall efficacy was the median of the efficacy grades of three items: symptoms, QoL and function. Chi-square test.

Table 6. Predictive Factors for Efficacy Using the Japanese Clinical Practice Guideline for Voiding Dysfunction

	Odds ratio		95% Confidence limits		P value	
	Group O (n = 37)	Group T (n = 39)	Group O (n = 37)	Group T (n = 39)	Group O (n = 37)	Group T (n = 39)
Age	1.077	1.14	0.98 - 1.19	0.99 - 1.33	NS	NS
PV	1.03	1.13	0.93 - 1.13	1.02 - 1.25	NS	0.021
Severity of symptoms	0.26	0.06	0.20 - 3.33	0.01 - 0.75	NS	0.029
Severity of QoL	0.59	7.02	0.09 - 3.67	0.70 - 70.72	NS	NS
Severity of dysfunction	0.30	1.26	0.06 - 1.51	0.18 - 8.70	NS	NS
Baseline BII	0.07	0.82	0.73 - 1.57	0.51 - 1.32	NS	NS

Logistic regression analysis.

difference in adverse events between the groups was identified. Diastolic blood pressure and systolic blood pressure were not significantly decreased in either group O or T, and the degree of change at 8 weeks in comparison to baseline showed no significant difference between the groups.

Discussion

Naftopidil was approved at an OD dosage [2]. Generally, OD dosing contributes to improved drug compliance. However, for elderly patients with many combination drugs, it is complicated to use TID and OD drugs together. Lipton et al compared a group that consulted a clinical pharmacist about their own medical treatment every 3 months and a group that did not. They reported that compliance was significantly improved in the group that consulted a clinical pharmacist, as they had fewer medications and less complex regimens [5].

Naftopidil may be administered in divided doses depending on the drug regimen of the individual patient, including the number of doses of concomitant drugs, to avoid a complicated dosage regimen. However, a difference in the dosage regimen may affect efficacy and tolerability. Therefore, the efficacy and tolerability of naftopidil 75 mg/day OD and 75 mg/day TID for LUTS/BPH were compared, and the factors predictive of efficacy with each dosage regimen were evaluated.

Naftopidil is an α1D/A-AR antagonist with higher selectivity for the α1D-AR subtype than for the α1A-adrenoceptor (α1A-AR) subtype [1]. Some reports have suggested that the α1D-AR subtype plays an important role in the regulation of bladder function [7-9]. Therefore, naftopidil is highly valued for the relief of storage symptoms, particularly nocturia [10]. For these reasons, group O was given the drug in the evening and group T was given the drug in the morning, afternoon and evening.

In this study, the subjective symptoms showed no significant differences between the two different dosage regimens, similar to our previous report [11]. However, VV, MFR and AFR were significantly improved between baseline and 8 weeks only in group O. The OD regimen was approximately equal in overall efficacy to the TID regimen. Extended-release alfuzosin 10 mg OD showed almost the same efficacy as 2.5 mg TID, although the dosage regimen was different [12]. In a comparative study of naftopidil 50 mg/day dosage regimens with OD administration in the morning and twice-daily (BID) administration in the morning and evening, the efficacy for subjective symptoms was approximately equal, but MFR showed that the effectiveness of the OD regimen started earlier than that of the BID regimen [13]. These reports were similar to the present results. Therefore, it was thought that the choice of 75 mg/day OD or 75 mg/day TID might be considered as combination therapy. However, it is necessary to consider a change to 75 mg/day OD for patients who show no improvements in objective findings with 75 mg/day TID.

No independent predictive factors that affected effectiveness were identified in group O, but PV and severity of symptoms were identified in group T. In other words, 75 mg/day TID of naftopidil was associated with an increased risk of lack of efficacy with large PV and slight symptoms. De la Rosette et al examined the re-treatment rate using follow-up data for up to 3 years for 316 of LUTS/BPH patients treated with an α1-blocker. They found that the re-treatment rate was significantly higher in patients with a PV > 40 mL at baseline, and tended to be high in patients with severe of subjective symptom [14]. It has been reported that IPSS and IPSS-QoL at baseline in the 3,514 LUTS/BPH patients given an α1-blocker for 6 months could not be used to predict the risk of acute urinary retention or re-treatment by operation [15]. In this way, there is no consensus about whether the severity of subjective symptoms at baseline is a predictive factor for the efficacy of α-1 blocker therapy. Some reports have described various α1-blockers as markedly more effective when subjective symptoms are severe at baseline, but the efficacy of α1-blockers might not be apparent with moderate symptoms at baseline [16, 17]. Further examination is necessary to determine whether the severity of subjective symptoms affects the effectiveness of α1 blockers.

On the other hand, PV at baseline is a predictive factor for the efficacy of α1-blockers [14, 18, 19]. PV was a predictive factor of the efficacy of naftopidil only in the 75 mg/day TID group, not in the 75 mg OD group in the present study. Nakashima et al reported that the concentration max (Cmax) of a single dose of naftopidil was dose-dependent, with a higher value seen with once-daily than with BID dosage [20]; this suggests that naftopidil OD allowed the achievement of a higher Cmax than the TID regimen. In addition, it was reported that maximal inhibition by the α1-blocker of the intraurethral pressure response correlated well with Cmax in anesthetized male dogs [21]. It was thought that only 75 mg/day OD might inhibit BOO regardless of PV based on these reports. However, it is a limitation of this study that the blood concentration of naftopidil was not measured, and future studies of the dosage regimen and relationships with factors predictive of the efficacy of naftopidil are needed.

The dosage method is often chosen from the viewpoint of compliance. However, it was thought that the dosage method affected the effectiveness based on the individual characteristics of patients in the present study. Therefore, the dosage regimen must be chosen based on the characteristics of the patients from the viewpoint of individual medical care. Based on the results of the present study, patients with a large PV should be given naftopidil with an OD dosage regimen.

Conclusions

Naftopidil 75 mg/day OD offered superior efficacy to 75 mg/

day TID in terms of objective findings, but the overall efficacy rate using criteria for treatment efficacy in BPH proposed by the Japanese Urological Association showed no significant difference between the two dosage regimens. Therefore, the dosage regimen of naftopidil can be chosen based on optimizing compliance. However, it is necessary to consider a change to the OD regimen for patients whose objective findings show no improvement with the TID regimen. In addition, in patients with a large prostate, the OD regimen should be chosen because its efficacy is not affected by PV.

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Conflict of Interest

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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