INTRODUCTION

It is necessary to evaluate the short-term efficacy of α1-adrenoceptor (AR) antagonist (α1-blockers; α1B) to relieve the patients from bother of male lower urinary tract symptoms/benign prostatic hyperplasia (mLUTS/BPH).
immediately, and if the initial treatment is not improvement, the next strategy should be thought.

Therefore, we evaluated following two points. First, the predictive factors which affect the efficacy of naftopidil 50 mg/day for 4 weeks (50 mg therapy) were evaluated. Second, the predictive factors which affect the efficacy of naftopidil dose increase to 75 mg/day therapy were evaluated.

MATERIALS AND METHODS

In this study, the inclusion criteria were age ≥50 years, prostate volume (PV) ≥20 mL, International Prostate Symptom Score (IPSS) ≥8, and IPSS quality of life (IPSS-QoL) score ≥3. The patients with the previous medical therapy were included in the study.

The exclusion criteria were patients who had prostatic cancer, urethral stricture, complications to influence on voiding function, high disease activity across the multiple organs, comprehension difficulties, and serious systemic condition. Moreover, the patients who are receiving other drugs affecting the urinary function were excluded. Patients judged by an attending physician to be inappropriate were also excluded from the study.

The sample size was calculated as follows. It was reported that the average of change in IPSS and standard deviation by the treatment of naftopidil was 5.9 and 5.8, respectively. Therefore, 13 patients were necessary so that it is 5% of considerable levels and 90% of statistical power. It was reported that the ineffective rate of naftopidil was about 40% by evaluation of the Japanese Urological Association (JUA) clinical guidelines for BPH. By these reports, we calculated that the necessary sample size was 81 patients.

This study was approved by the Institutional Review Board of Hokkaido Social Welfare Association Hakodate Hospital and agreed to by all participating patients.

Ninety-two patients diagnosed with clinical mLUTS/BPH from July 2006 to May 2013 were enrolled. Nine patients were withdrawn from participation, including two for nonadherence, one with prostate cancer, one who was visited another hospital by comorbidity, one who was not measured the objective findings, and four who failed to make follow-up visits. Thus, efficacy was analyzed in a total of 83 patients.

Naftopidil was administered at an initial dose of 50 mg/day for 4 weeks and increased to 75 mg/day for further 4 weeks. Age and PV were evaluated at the start of treatment. IPSS, IPSS-QoL, voided volume, maximum flow rate (MFR), and postvoid residual (PVR) urine volume were evaluated at baseline, week 4, and week 8.

The evaluation of efficacy was defined using the criteria in the JUA clinical guidelines for BPH. It was as follows.

1. The efficacy for symptom was classified by the ratio with post- and pre-treatment of IPSS as excellent: ≤0.25, good: ≤0.5, fair: ≤0.75, and poor/worse: >0.75.
2. The efficacy for QoL was classified by the changes in pre- and post-treatment of IPSS-QoL as excellent: ≥4, good: 3, fair: 2 or 1, and poor/worse: ≤0. The efficacy for function was classified by the changes in post- and pretreatment of MFR as excellent: ≥10 mL/s, good: ≥5 mL/s, fair: ≥2.5 mL/s, and poor/worse: ≤0.5 mL/s.
3. Overall efficacy is the median of efficacy grade of three items as symptom, QoL, and function. Moreover, the patients who were evaluated excellent, good, or fair by overall efficacy were judged effective group, and the patients who were evaluated poor/worse by overall efficacy were judged worse group in this study.

At week 4, the patients were divided into an effective and an ineffective group in 50 mg therapy (Group E and Group I, respectively). For further 4 weeks, the dosage of naftopidil was increased to 75 mg/day in all patients. At week 8, the patients in Group E were divided into an effective and an ineffective group in this dose increase therapy (Group EE and Group EI, respectively). The patients in Group I were divided into an effective and an ineffective group, too (Group IE and Group II, respectively).

The intragroup data were analyzed by the paired t-test or the Wilcoxon signed-rank test. The intergroup data were analyzed by the unpaired t-test or the Mann–Whitney U-test. The Logistic-regression analysis was used to identify the predictive factors. The effective and ineffective groups were applied as a dependent variable. IPSS-QoL, MFR, and PVR were applied as an independent variable. To avoid any confounding, only three subjective symptom scores of IPSS post-micturition symptoms subscore (incomplete emptying; IPSS PMS), IPSS storage symptoms subscore (frequency, urgency, and nocturia; IPSS-SS), and IPSS voiding symptoms subscore (intermittency, weak stream, and straining; IPSS-VS) were applied as an independent variable. This independent variable at week 4 and the amount of change from baseline to week 4 were defined as the baseline variable and the dynamic variable of this dose increase therapy, respectively. P < 0.05 was considered statistically significant.
RESULTS

Distribution of the group and baseline characteristics
Forty six patients (55.4%) were effective (Group E), and 37 patients (44.6%) were ineffective (Group I) in 50 mg/day therapy for 4 weeks. In Group E, 38 patients (45.8%) were effective (Group EE), and 8 patients (9.6%) were ineffective (Group EI) in the dose increase therapy for 8 weeks. In Group I, 17 patients (20.5%) were effective (Group IE), and 20 patients (24.1%) were ineffective (Group II) in the dose increase therapy [Figure 1]. In this dose increase therapy, 55 patients (66.3%) showed improvement of overall efficacy [Table 1]. Only PVR in baseline characteristics was significantly larger in the Group I compared with the Group E [Table 2].

The predictive factors which affected the efficacy of 50 mg therapy
Groups E and I were applied as the dependent variable. The predictive factor which affected the efficacy of 50 mg therapy was large PVR at baseline [odds ratio (OR): 1.013, \( P = 0.012 \), Figure 2]. All parameters of change in subjective symptoms and objective findings, except MFR at week 8 and PVR at weeks 4 and 8, were significantly improved in Group E compared with Group I [Table 3].

The predictive factors which affected the efficacy of dose increase therapy in Group E
When Groups EE and EI were applied as the dependent variable and the baseline variables at the time of 75 mg/day dosage starts were applied as the independent variable, there was no predictive factor which affected the efficacy of dose increase therapy [Figure 3a]. On the other hand, when the dynamic variables that were the amount of change from baseline to week 4 were applied as the independent variable, the predictive factor which affected the efficacy of dose increase therapy was change in IPSS-SS from baseline to week 4 [OR: 2.137, \( P = 0.024 \), Figure 3b].

The predictive factors which affected the efficacy of dose increase therapy in Group I
When Groups IE and II were applied as the dependent variable and the baseline variables at the time of 75 mg/day dosage starts were applied as the independent variable, there was no predictive factor which affected the efficacy of dose increase therapy [Figure 4a]. On the other hand, when the dynamic variables that were the amount of change from baseline to week 4 were applied as the independent variable, the predictive factor which affected the efficacy of dose increase therapy was change in MFR from baseline to week 4 [OR: 0.817, \( P = 0.045 \), Figure 4b].

DISCUSSION

The treatment for mLUTS/BPH including in \( \alpha_{1B} \) is important to relieve the patients from bother immediately. Therefore, it is necessary to know the predictive factors which affect the efficacy of short-term \( \alpha_{1B} \) therapy. However, there were few reports about the predictive

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**Figure 1:** Distribution of patients. The patients were divided into four groups which were effective and ineffective. The evaluation of efficacy was defined using the criteria in the Japanese Urological Association clinical guidelines for benign prostatic hyperplasia. The patients who were evaluated excellent, good, or fair by overall efficacy were judged effective group, and the patients who were evaluated poor/worse by overall efficacy were judged ineffective group.
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Factors of short-term α1B therapy though there were some long-term reports of it."^[4,6] α1D/A-AR antagonist, naftopidil, was recommended to “highly recommended to do” in the JUA clinical guidelines for BPH[^3] and is widely used for mLUTS/BPH treatment in Japan, Korea, China, and India.[^4] The standard dose of naftopidil is recommended with 50 and 75 mg/day;[^8] many reports choose 50 mg/day of naftopidil for a maintenance dose.[^9] Recently, the efficacy of naftopidil dose increase therapy from 50 to 75 mg/day was evaluated for the patients who were ineffective in 50 mg/day.[^10,11] However, it is unknown about the predictive factors which affect the efficacy of naftopidil dose increase therapy. Hence, we examined the predictive factors which affect the efficacy of naftopidil short-term therapy and dose increase therapy. In this study, it was the characteristic that the predictive factors were evaluated by the baseline variable and the dynamic variable.

*Table 1: Evaluation of efficacy using the Japanese Urological Association clinical guidelines for benign prostatic hyperplasia*

| Group | Overall efficacy | Week 4 | Week 8 |
|-------|------------------|--------|--------|
| Group E | Excellent | 5 | Group EE | Excellent | 2 |
| | Good | 13 | | Good | 2 |
| | Poor/worse | 28 | | Poor/worse | 0 |
| Group I | Poor/worse | 37 | Group EI | Poor/worse | 3 |
| | Good | 1 | | Good | 9 |
| | Fair | 12 | | Fair | 14 |
| Overall efficacy rate | 55.4% (46/83) | Group II | Overall efficacy rate | 66.3% (55/83) |

The patients who were evaluated excellent, good, or fair by overall efficacy were judged effective group, and the patients who were evaluated poor/worse by overall efficacy were judged ineffective group. Group E: Effective group in 50 mg therapy, Group I: Ineffective group in 50 mg therapy, Group EE: Effective group in this dose increase therapy in Group E, Group EI: Ineffective group in this dose increase therapy in Group E, Group IE: Effective group in this dose increase therapy in Group I, Group II: Ineffective group in this dose increase therapy in Group I

*Table 2: Baseline characteristics*

| All patients (n) | Group E (n) | Group I (n) | P (intergroup) |
|------------------|-------------|-------------|---------------|
| Age (years) | 71.0±8.8 (83) | 70.2±9.2 (46) | 72.1±8.2 (37) | NS |
| PV (mL) | 40.9±24.4 (81) | 38.4±24.3 (44) | 43.9±24.6 (37) | NS |
| PSA (ng/mL) | 3.18±7.32 (74) | 4.00±9.61 (41) | 2.6±2.26 (33) | NS |
| IPSS total score | 16.0±6.2 (83) | 165±6.1 (46) | 15.5±6.4 (37) | NS |
| IPSS-SS | 7.3±2.8 (83) | 7.2±2.6 (46) | 7.5±3.0 (37) | NS |
| IPSS-VS | 6.5±4.4 (83) | 7.0±4.6 (46) | 5.9±4.1 (37) | NS |
| IPSS-QoL | 4.7±1.0 (83) | 4.7±0.9 (46) | 5.9±4.1 (37) | NS |
| Voided volume (mL) | 178.3±117.6 (83) | 168.5±107.5 (46) | 190.4±129.5 (37) | NS |
| MFR (mL/s) | 12.3±7.0 (83) | 12.0±6.1 (46) | 12.7±8.0 (37) | NS |
| PVR (mL) | 55.2±63.4 (83) | 37.2±44.3 (46) | 77.5±76.0 (37) | 0.006 |

MFR, PVR: Unpaired t-test, others: Mann-Whitney U-test. IPSS-PMS: Postmicturition symptoms (incomplete emptying) score, IPSS-SS: IPSS storage symptoms subscore, IPSS-VS: IPSS voiding symptoms subscore, MFR: Maximum flow rate, PVR: Postvoid residual urine volume, PV: Prostate volume, PSA: Prostate-specific antigen, QoL: Quality of life, NS: Not significant

*Figure 2: The predictive factors which affected the efficacy of 50 mg/day for 4 weeks. The Logistic-regression analysis was used to identify the predictive factors. Group E (n = 46) and Group I (n = 37) were applied as a dependent variable. The predictive factor was large PVR at baseline. Closed circle: Odds ratio, horizontal line: 95% confidence interval

Overall efficacy rate of 50 mg therapy is 55.4% in this study. There were some reports that the effective ratio of naftopidil monotherapy for 8–12 weeks were 50.8%, 52.5% and 68.6%.[^10,12] Therefore, it thought that this result was appropriate. Nevertheless, Mizusawa et al. reported that the effective ratio of naftopidil for 4 weeks of administration was 23.9%.[^13] They decided the responders using original
questionnaire of treatment satisfaction. On the other hand, we decided the responders using the criteria of the JUA clinical guidelines for BPH in this study. Hence, these should not compare these reports with this study simply.

Figure 3: The predictive factors which affected the efficacy of dose increase therapy in Group E. The Logistic-regression analysis was used to identify the predictive factors. Groups EE (n=38) and EI (n=8) were applied as the dependent variable. (a) The baseline variables at the time of 75 mg/day dosage starts were applied as the independent variable. There was no predictive factor. (b) The dynamic variables that were the amount of change from baseline to week 4 were applied as the independent variable. The predictive factor was change in IPSS-SS from baseline to week 4

Table 3: Change in subjective symptoms and objective findings (Group E and Group I)

|                  | Group E (46) | Group I (37) | P (intergroup) |
|------------------|--------------|--------------|----------------|
| IPSS total score|              |              |                |
| Week 4           | -8.0±5.5     | 0.3±5.5      | <0.001         |
| Week 8           | -9.0±6.4     | -2.4±6.1     | <0.001         |
| P (intragroup)   | 0.040        | 0.023        | -              |
| IPSS-PMS         |              |              |                |
| Week 4           | -1.3±1.5     | 0.2±1.6      | <0.001         |
| Week 8           | -1.4±1.6     | -0.6±1.5     | 0.036          |
| P (intragroup)   | NS           | NS           | -              |
| IPSS-SS          |              |              |                |
| Week 4           | -3.1±2.6     | -0.5±2.7     | <0.001         |
| Week 8           | -3.4±3.0     | -0.8±2.5     | <0.001         |
| P (intragroup)   | NS           | NS           | -              |
| IPSS-VS          |              |              |                |
| Week 4           | -3.5±4.3     | 0.6±3.8      | <0.001         |
| Week 8           | -4.2±4.4     | -0.8±3.6     | 0.001          |
| P (intragroup)   | NS           | 0.017        |                |
| IPSS-QoL         |              |              |                |
| Week 4           | -2.0±1.5     | -0.6±1.4     | <0.001         |
| Week 8           | -2.5±1.6     | -0.8±1.1     | <0.001         |
| P (intragroup)   | 0.022        | NS           |                |
| MFR (mL/s)       |              |              |                |
| Week 4           | 3.0±7.4      | -2.0±4.6     | <0.001         |
| Week 8           | 3.6±7.1      | 2.0±10.0     | NS             |
| P (intragroup)   | NS           | NS           |                |
| PVR (mL)         |              |              |                |
| Week 4           | -0.7±48.2    | 4.1±99.6     | NS             |
| Week 8           | -6.5±46.7    | -12.5±72.5   | NS             |
| P (intragroup)   | NS           | NS           |                |

MFR, PVR: Unpaired t-test (intergroup), paired t-test (intragroup), others: Mann-Whitney’s U-test (intergroup), Wilcoxon signed-rank test (intragroup). PMS: Postmicturition symptoms (incomplete emptying) score, SS: Storage symptoms score, VS: Voiding symptoms score, MFR: Maximum flow rate, PVR: Postvoid residual urine volume, QoL: Quality of life, NS: Not significant, IPSS: International Prostate Symptom Score
Large PVR at baseline was a predictive factor which affected the efficacy of 50 mg therapy. IPSS and PVR at baseline were predictive factors of symptom progression in the Alfuzosin Long-Term Efficacy and Safety Study for 2 years which compared alfuzosin with the placebo.[14] Kawachi et al. reported that the treatment failure rate of α1B for 4 years was affected by PV, PVR, history of acute urinary retention, and complications of overactive bladder (OAB) at baseline.[15] PVR at baseline is a predictive factor for not only the long-term treatment but also the short-term treatment of α1B. Therefore, the patients with large PVR should choose the treatment except 50 mg therapy or combination with the drug that has other mechanisms.

PV at baseline was not a predictive factor for the efficacy of 50 mg therapy in this study. There are some reports that patients with a larger PV have a higher risk of long-term α1B monotherapy failure.[14-16] There were the reports that baseline PV did not affect the efficacy of the short-term α1B therapy.[12,14] Furthermore, we reported that the improvement of IPSS, IPSS-QoL, and MFR did not have a difference in large PV group (PV ≥40 mL) and small PV group (PV <40 mL) for 50 mg therapy.[17] PV at baseline might be a predictive factor for efficacy of the long-term treatment but not the short-term treatment of α1B.

In Group E, there was no predictive factor in baseline variables, and the amount of change from baseline to week 4 in IPSS-SS might be a predictive factor for the efficacy of 75 mg/day dose increase therapy.

There is a report that 45% of mLUTS/BPH patients had both bladder outlet obstruction (BOO) and detrusor overactivity (DO).[18] BOO was associated with DO by various factors such as ischemia, and DO is a frequent cause of OAB symptoms. However, there is a report that BOO and OAB may be caused independently in mLUTS/BPH.[19] Higher IPSS-SS score suggests OAB. Naftopidil has a higher affinity for α1D-AR subtype than α1A-AR subtype.[20] α1D-AR subtype regulated the bladder functions,[21,22] and there was a report that naftopidil is particularly effective for storage symptoms (SSs) by the inhibition of α1D-AR subtype.[9] Hence, in the patients who were ineffective in IPSS-SS by naftopidil, it is suggested that a cause of the
SSs might be other factors independent of bladder function regulated by α1D-AR subtype. The patients that IPSS-SS was ineffective by 50 mg therapy might need to change it into other treatments. However, a large-scale study is necessary because the sample size is small in this study.

In Group I, there was no predictive factor in the baseline variables, and the amount of change from baseline to week 4 in MFR might be a predictive factor in the dynamic variable which affected the efficacy of 75 mg/day dose increase therapy. However, the sample size is small in Groups IE and II. It is a limitation in this study.

It is interesting that the predictive factors of this dose increase therapy were the dynamic variables, but not the baseline variables. There is a report that improvement of IPSS, IPSS-VS, urgency, and slow stream was already shown at the dose of 50 mg/day in the patients who were effective after naftopidil dose increase to 75 mg/day. This report showed that the predictive factors were the dynamic variables like this study. Therefore, the prediction of efficacy for dose increase therapy should pay attention to the dynamic variable in the treatment during 50 mg therapy.

CONCLUSIONS

We showed that large PVR at baseline was a predictive factor which affected the efficacy of 50 mg therapy. The short-term efficacy of 50 mg therapy was ineffective for the patients who had large PVR at baseline.

The predictive factor of this dose increase therapy might be a dynamic variable in 50 mg/day of dose period, but not a baseline variable at the time of 75 mg/day dosage starts. Therefore, if dose increase to 75 mg/day was considered, it should not be judged from baseline variables at the start of 75 mg/day dosage starts and should be judged by the change of variables during 50 mg therapy periods.

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Conflicts of interest

There are no conflicts of interest.

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