Does prostate volume affect the efficacy of α1D/A: Adrenoceptor antagonist naftopidil?

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Abstract

Introduction: There have been reports that one of the factors affecting the efficacy of α1-adrenoceptor antagonists (α1-blocker; α1-B) was prostate volume (PV). However, there are few reports of short-term prospective trials comparing the efficacy of α1-B by PV. We examined the influence of PV on the short-term efficacy of naftopidil dose increase therapy to administration of 75 mg/day after an initial dose of 50 mg/day.

Materials and Methods: A total of 85 patients with lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) received 50 mg/day of naftopidil for 4 weeks. After 4 weeks, the dosage of naftopidil was increased to 75 mg/day for a further 4 weeks. We divided the patients into two groups of PV ≥40 mL at baseline (Group L) and PV <40 mL at baseline (Group S).

Results: International Prostate Symptom Score (IPSS), IPSS storage symptoms, and IPSS quality-of-life score were significantly improved at 4 and 8 weeks compared with baseline in both Groups. IPSS voiding symptoms (IPSS-VS) were significantly improved at 4 and 8 weeks compared with baseline in Group S. IPSS and IPSS-VS were significantly improved at 8 weeks compared with 4 weeks only in Group L. IPSS-VS and intermittency at 4 weeks were significantly decreased in Group S compared with Group L. Maximum flow rate was significantly improved at 8 weeks compared with baseline in Group L.

Conclusions: PV is a predictive factor affecting the efficacy of naftopidil 50 mg/day for IPSS-VS, and the dose increase to 75 mg/day effective for IPSS-VS. A total of 50 mg/day of naftopidil is the maintenance dose for LUTS/BPH patients with a small PV, and 75 mg/day of dose increase therapy should be chosen for patients with a large PV.

Key Words: Dose increase therapy, naftopidil, prostate volume

INTRODUCTION

α1-adrenoceptor antagonist (α1-blocker; α1-B) is recommended as the first-line medical treatment for lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH) by Japanese clinical guidelines for BPH.¹ There have been reports that one of the factors affecting the efficacy of α1-B was prostate volume (PV).²³ There have been similar reports about naftopidil.⁴⁻⁸ However, these reports were of long-term studies or sub-analysis of the examination, so there are few reports of short-term prospective trials comparing the efficacy of naftopidil by PV.

On the other hand, the efficacy of naftopidil was dose-dependent, and safety was comparable.⁹⁻¹⁰ There are many reports choosing 50 mg/day as a maintenance dosage of naftopidil.¹¹⁻¹² In
addition, there have recently been some reports of naftopidil dose increase therapy.\(^{[5-7]}\)

In this prospective study, we examined the influence of PV on the short-term efficacy of naftopidil dose increase therapy to administration of 75 mg/day after an initial dose of 50 mg/day.

**MATERIALS AND METHODS**

Eighty-five patients who received a diagnosis of clinical LUTS/BPH from July 2006 to May 2013 were enrolled in this study. The inclusion criteria were age ≥50 years, PV ≥20 mL, International Prostate Symptom Score (IPSS) ≥8, and IPSS quality-of-life score (IPSS-QoL) ≥3. The exclusion criteria were patients who had prostate cancer, bladder outlet obstruction (BOO), disease activity across multiple organs suspected serious conditions, comprehension difficulties, and those who were serious conditions receiving α1-B for hypertension. Patients judged by the attending physician to be inappropriate were also excluded.

Naftopidil was administered at an initial dose of 50 mg/day for 4 weeks and was increased to 75 mg/day for a further 4 weeks. The age, PV, IPSS, IPSS-QoL, voided volume (VV), maximum flow rate (Qmax), and postvoid residual urine volume (PVR) were evaluated before the start of treatment. IPSS, IPSS-QoL, VV, Qmax, and PVR were evaluated after 4 and 8 weeks. The enrolled patients were separated by PV at baseline into two groups. This dose increase therapy was approved by the Institutional Review Board of Hokkaido Social Welfare Association Hakodate Hospital and agreed to by all participating patients.

The paired t-test was used to compare Qmax and PVR between baseline and 4 or 8 weeks. The unpaired t-test was used to compare age, PV, PSA, Qmax, and PVR between groups. For all other parameters, the Wilcoxon signed-rank test was used for comparisons between baseline and 4 or 8 weeks while the Mann–Whitney U-test was used for comparisons between groups.

**RESULTS**

Of the 85 patients who were enrolled, 16 were withdrawn from participation, including 1 for noncompliance, 1 with prostate cancer, 1 who was visited to another hospital by comorbidity, 1 who was not measured the objective findings, 4 who failed to make follow-up visits and 8 who were PV <20 mL. Thus, efficacy was analyzed in a total of 69 patients. The 69 patients were separated into 29 patients with a PV ≥40 mL (large prostate group; Group L) and 40 patients with a PV <40 mL (small prostate group; Group S).

The characteristics of the patients are summarized in Table 1. PV was significantly larger in Group L than Group S, and PVR was significantly higher in Group L than Group S. Other parameters have no significant differences between the two groups.

All patients with changes in IPSS, IPSS storage symptoms (IPSS-SS), IPSS voiding symptoms (IPSS-VS) or IPSS-QoL as the subjective symptoms, and Qmax or PVR as the objective findings are shown in Figure 1. All parameters of the subjective symptoms were significantly improved at 4 and 8 weeks compared with baseline. IPSS and IPSS-VS were significantly improved at 8 weeks compared with 4 weeks. Qmax was significantly improved at 8 weeks, but PVR was not improved compared with baseline.

International Prostate Symptom Score and IPSS-QoL were compared between Group L and Group S [Figure 2]. IPSS and IPSS-QoL were significantly improved at 4 and 8 weeks compared with baseline in both Groups. IPSS was significantly improved at 8 weeks compared with 4 weeks only in Group L. There were no significant differences between the two groups.

International Prostate Symptom Score-storage symptoms and IPSS-VS were compared between both groups [Figure 3]. IPSS-SS was significantly improved at 4 and 8 weeks compared with baseline in both groups. There were no significant differences between the two groups. IPSS-VS were significantly improved at 4 and 8 weeks compared with baseline in Group S. However, there was no significant improvement at 4 weeks but there was significant improvement at 8 weeks in Group L.

IPSS-VS were significantly improved at 8 weeks compared with 4 weeks only in Group L. Improvement of IPSS-VS at 4 weeks was significantly higher in Group S compared with Group L.

![Table 1: Characteristics](image-url)

|                | All patients | Group L | Group S | P     |
|----------------|--------------|---------|---------|-------|
| Age (years)    | 70.9±8.4     | 69      | 69      | 0.036 |
| PV (mL)        | 43.6±24.9    | 69      | 69      | <0.001|
| PSA (ng/mL)    | 2.6±3.4      | 65      | 27      | 0.003 |
| IPSS           | 16.1±6.0     | 69      | 69      | 0.003 |
| IPSS-SS        | 7.1±2.6      | 69      | 7.3±2.5 | 0.036 |
| IPSS-VS        | 6.7±4.3      | 69      | 7.1±4.3 | 0.003 |
| IPSS-QoL       | 4.7±1.0      | 69      | 4.5±0.9 | 0.028 |
| VV (mL)        | 164.7±114.6  | 69      | 169.7±109.3 | 0.046 |
| Qmax (mL/s)    | 11.9±7.4     | 69      | 11.0±5.7 | 0.028 |
| PVR (mL)       | 60.8±67.2    | 69      | 81.6±71.3 | 0.028 |

PV was significantly larger in Group L than Group S, and PVR was significantly higher in Group L than Group S. PV: Prostate volume, PSA: Prostate specific antigen, IPSS: International Prostate Symptom Score, IPSS-SS: International Prostate Symptom Score storage symptoms, IPSS-VS: International Prostate Symptom Score voiding symptoms, IPSS-QoL: International Prostate Symptom Score quality-of-life score, VV: Voided volume, Qmax: Maximum flow rate, PVR: Postvoid residual, SD: Standard deviation.
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Each of the seven symptoms in IPSS was compared between both groups [Table 2]. In Group L, urgency and straining were not significantly improved at 8 weeks compared with baseline. However, all parameters were significantly improved at 8 weeks compared with baseline in Group S. Intermittency was significantly improved at 8 weeks compared with 4 weeks in the Group L. Incomplete emptying and nocturia were significantly improved at 8 weeks compared with 4 weeks in Group S. All seven symptoms of parameters at 8 weeks were no significant differences between the two groups. Improvement of intermittency at 4 weeks was significantly higher in Group S compared with Group L.

Maximum flow rate and PVR were compared between both groups [Figure 4]. Qmax was significantly improved at 8 weeks compared with baseline in Group L. PVR at baseline and 4 weeks was significantly higher in Group L compared with the Group S and was not significantly improved at 4 and 8 weeks compared with baseline in both groups.

DISCUSSION

α1-B is the first-line medical treatment for LUTS/BPH. However, the treatment strategy of α1-B may not be necessarily considered by the predictive factors of efficacy. There have been some reports about the predictive factors of the efficacy of α1-B. It has been reported that the re-treatment rate of LUTS/BPH patients who were given α1-B for 5 years was affected by urodynamically proven BOO and an enlarged prostate at baseline.

In a study of clinical baseline factors that affect long-term treatment failure, 110 patients who had surgical treatment following α1-B medication had a significantly higher IPSS and larger PV at baseline compared with 337 patients who continued with the α1-B. Masumori et al. reported that LUTS/BPH patients with a large PV of >35 mL had a significantly higher treatment failure rate in the treatment with naftopidil for 4 years. Likewise, there have been many reports that PV was one of the predictive factors affecting the long-term efficacy of α1-B. On the other hand, a few prospective studies reported that PV affected the efficacy of short-term treatment of naftopidil. However, these reports were sub-analysis of the examination of patients who were poor responders to naftopidil 50 mg/day or comparison between once-daily and thrice-daily administration.
In this prospective study, we examined the influence of PV on the short-term efficacy of naftopidil dose increase therapy. Hong et al. reported that one of the predictive factors of α1-B monotherapy failure was PV and the cut-off level was 35.65 mL. de la Rosette et al. and Masumori et al. divided PV into two groups with cut-off levels of 40 mL and 35 mL, respectively, and evaluated the predictive factors of α1-B treatment. In addition, the EAU recommended in 2012 that men with enlarged prostates, especially those >40 mL, use 5α-reductase inhibitors. There are various reports about the cut-off level of PV. We divided the cut-off into PV ≥40 mL because the average PV in this study was >40 mL.

Subjective symptoms at 4 and 8 weeks were improved in comparison with baseline in all patients. Qmax was not improved at 4 weeks but was improved at 8 weeks compared with baseline in this study. It was reported that patients who had unsatisfactory improvement of their QoL from naftopidil 50 mg/day received an increase to 75 mg/day. In that report, IPSS-VS was significantly improved by the dose increase to 75 mg/day. That report almost accords with our results. Thus, the naftopidil dose increase therapy is effective for LUTS/BPH.

International Prostate Symptom Score and IPSS-VS were improved at 8 weeks compared with 4 weeks, but IPSS-SS was not improved in all patients, so this dose increase therapy may be more effective for voiding symptoms than storage symptoms. α1D/A-adrenoceptor antagonist naftopidil has a relatively high affinity for the α1D-AR subtype, and the α1D-AR subtype...
has a role in regulating bladder function in vivo.[16,17] Thus, naftopidil has attracted attention for improvement of storage symptoms or nocturia.[16] On the other hand, the distribution of the α1d-AR subtype is approximately equal to the α1a-AR subtype in the prostate.[19] Naftopidil improves BOO by the inhibition of the α1D-AR subtype distributed in the prostate. The difference in efficacy between storage symptoms and voiding symptoms are understood if the drug sensitivity of the α1D-AR subtype in the prostate is different from in the bladder, but that remains to be seen. In the meantime, naftopidil was effective for voiding symptoms by dose increase therapy to 75 mg/day, and it was thought that this contributes to the efficacy for improvement of IPSS.

In both groups, similar efficacy was shown at 8 weeks of naftopidil dose increase therapy for IPSS, IPSS-SS, QoL, and Qmax, regardless of PV. However, efficacy for IPSS- VS was not shown in the first 4 weeks of administration of 50 mg/day in Group L. Two reasons were thought to cause this result. The efficacy for IPSS-VS of 50 mg/day is limited in patients with a large PV, and if administration of 50 mg/day is extended in Group L for >4 weeks, 50 mg/day may be effective for patients with a large PV. Mizusawa et al. have shown that patients who were poor responders to 50 mg/day of naftopidil had higher voiding symptoms at baseline than patients who were good responders, and they suggested the possibility that dose increase therapy could relax the prostate/urethra smooth muscle.[5] Funahashi et al. examined dose increase therapy for poor responders to 50 mg/day of naftopidil. PV was larger in poor responders than good responders to 50 mg/day, and the study showed the efficacy of dose increase therapy for patients with a large PV.[6] In addition, the dosage was increased to 75 mg/day after 4 weeks, and IPSS and IPSS-VS were improved at 8 weeks compared with 4 weeks in this study. Therefore, it was thought that the efficacy of naftopidil 50 mg/day was limited in patients who had a large PV.

On the other hand, a limitation of this study was not being able to evaluate the period of efficacy expression with the 50 mg/day maintenance therapy for patients who had a large PV and the need for dose increase therapy in patients who had a small PV, because 50 mg/day maintenance therapy was not examined. However, it is necessary to consider the dose increase therapy by the early evaluation of subjective symptoms and objective findings in Group L.

It was reported that the good responders to naftopidil 50 mg/day had a smaller PV than poor responders. Furthermore, the efficacy of 50 mg/day of naftopidil is better after 8 weeks rather than 4 weeks, so naftopidil 50 mg/day should be continued for 8 weeks.[7] Therefore, 50 mg/day of naftopidil maintenance therapy may be sufficient for a patient with a small PV.

Postvoid residual at 4 weeks was significantly decreased in Group S compared with Group L. The evaluation of the influence on PVR of PV was difficult in this study, because PVR at baseline was significantly higher in Group L compared with Group S. However, it has been reported that PV was correlated with PVR.[20] In this present study, a correlation of PV and PVR was suggested because PVR at baseline was significantly higher in Group L compared with Group S. It was thought that the reason that PVR in Group L was higher than Group S at baseline was a correlation of PVR and PV.

We currently have many kinds of treatment strategies, including dose increase in drug administration, switching to another drug or additional therapy with a different mechanism. In general, it is possible to increase the dose of naftopidil to 75 mg/day because the maintenance dose is 50 mg/day. This dose increase therapy of naftopidil has shown that subjective symptoms were improved after 4 and 8 weeks compared with baseline in Group S, IPSS, and IPSS-VS were improved at 8 weeks compared with 4 weeks in Group L, and improvement of IPSS-VS at 4 weeks was significantly higher in Group S compared with Group L.

**CONCLUSION**

Our present study found that PV is a predictive factor affecting the efficacy of naftopidil 50 mg/day for subjective symptoms, particularly voiding symptoms, and the dose increase to 75 mg/day is effective for IPSS-VS. Therefore, 50 mg/day of naftopidil is the maintenance dose for LUTS/BPH patients with a small PV, and 75 mg/day dose increase therapy should be chosen for patients with a large PV.

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