Sympotms Predictive for Efficacy of Naftopidil in Patients with Benign Prostate Hyperplasia

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Objectives: To evaluate the lower urinary tract symptoms predicting the efficacy of the α1-adrenoreceptor (AR) antagonist naftopidil in patients with benign prostate hyperplasia.

Methods: The efficacy of naftopidil was examined on the basis of changes in the international prostate symptom score (IPSS). All patients received naftopidil (50 mg/day) for 12 weeks. We defined a “responder” as a patient whose total IPSS improved by five or more points and assessed the lower urinary tract symptoms predicting the efficacy of treatment by performing multivariate and probit analyses.

Results: Among 132 patients whose data could be analyzed, the efficacy rate was 50.8%. All IPSS items except the urgency score were significantly higher in the responders than the non-responders before treatment, and all IPSS items were lower in the responders after treatment. In the responder group, significant improvements were observed in the total IPSS score, quality of life (QOL) index, maximum flow rate (Qmax), residual urine volume, and all IPSS items after treatment. In contrast, in the non-responder group, no parameter except the QOL index improved significantly. The probit analysis demonstrated that the score for weak stream (≥ 3) or nocturia (≥ 4) in the IPSS were factors predicting an effective response to naftopidil treatment.

Conclusions: Weak stream and/or nocturia are the key symptoms that predict the efficacy of naftopidil treatment in patients with benign prostatic hyperplasia. Those with a score of ≥ 3 for weak stream or of ≥ 4 for nocturia are expected to achieve a good response in the subjective symptoms with administration of naftopidil.

Key words: benign prostatic hyperplasia, clinical trial, drug therapy, international prostate symptom score, naftopidil

1. INTRODUCTION

The number of patients seeking medical care and complaining of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) has recently been increasing in the aging population. The management of such patients includes pharmacologic and surgical options, and the type of treatment depends on the severity of the subjective symptoms and objective findings.1,2 Standard drugs used in pharmacologic treatments include α1-adrenoreceptor (AR) antagonists and 5α-reductase inhibitors, which are recommended for use alone or in combination in patients with moderate to severe symptoms. The α1-AR antagonists relieve not only voiding but also storage symptoms.3-8 Treatment with α1-AR antagonists generally leads to rapid improvement in LUTS and has a low rate of adverse events; thus, these agents are commonly used as a first-line treatment for LUTS associated with BPH.1,9

Several α1-AR antagonists such as tamsulosin, naftopidil and silodosin have been approved for the treatment of BPH in Japan; of these, tamsulosin has a higher affinity to the α1A-AR subtype and naftopidil has a higher affinity for the α1D-AR subtype, while silodosin is almost purely selective for the α1A-AR subtype.10,11 The effectiveness of naftopidil both in subjective symptoms and objective findings is reported in many studies; however, the patients’ factors that predict the efficacy of drug administration have received scant attention.

We conducted a prospective study to assess the efficacy of naftopidil on the basis of the international prostate symptom score (IPSS) and investigate the symptoms which predict the efficacy of naftopidil in the treatment of patients with BPH.

2. METHODS

The present study was conducted as a prospective, open-labeled, multicenter study. The study protocol was evaluated and approved by the ethics committee at Nagoya University Graduate School of Medicine prior to initiation. All patients provided written informed consent in order to be enrolled in this study.

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2.1. Patient enrollment

This study included 196 patients with diagnosed but untreated BPH who visited our hospital with a complaint of LUTS between April 2007 and December 2009. Participants had to meet the following conditions: (i) 50–80 years of age; (ii) IPSS ≥8 and quality of life (QOL) index < five points in this study. We obtained the IPSS-QOL index as a responder as a patient whose IPSS improved by less than five or more points and a “non-responder” as a patient whose IPSS improved by five or more points and a “non-responder” as a patient whose IPSS improved by less than five or more points in this study. We obtained the IPSS-QOL index and measured $Q_{\text{max}}$ by uroflowmetry, residual urine volume with transabdominal ultrasonography, and prostate volume with transabdominal or transrectal ultrasonography. We administered naftopidil at a dose of 50 mg/day (once a day) for 12 weeks to patients who met the aforementioned criteria, and then recorded the changes in the following parameters compared to baseline values: (i) subjective symptoms (total IPSS, individual scores of IPSS items and QOL index) and (ii) objective parameters ($Q_{\text{max}}$ on uroflowmetry and residual urine volume).

2.2. Study protocol

The efficacy of naftopidil was evaluated on the basis of changes in the subjective symptoms estimated using IPSS. The American Urological Association guideline reported that mean changes from the baseline in IPSS ranged between 4 and 6 on the basis of the meta-analysis of reports concerned with the efficacy of various $\alpha$1-AR antagonists for BPH patients.1 On the basis of the result of this meta-analysis, we defined a “responder” as a patient whose IPSS improved by five or more points and a “non-responder” as a patient whose IPSS improved by less than five points in this study. We obtained the IPSS-QOL index and measured $Q_{\text{max}}$ by uroflowmetry, residual urine volume with transabdominal ultrasonography, and prostate volume with transabdominal or transrectal ultrasonography. We administered naftopidil at a dose of 50 mg/day (once a day) for 12 weeks to patients who met the aforementioned criteria, and then recorded the changes in the following parameters compared to baseline values: (i) subjective symptoms (total IPSS, individual scores of IPSS items and QOL index) and (ii) objective parameters ($Q_{\text{max}}$ on uroflowmetry and residual urine volume).

2.3. Statistics

All values are presented as means ± standard deviation. The Mann–Whitney $U$-test was used to compare the baseline IPSS between the groups. Changes in IPSS and uroflowmetric values were analyzed using a stratified Wilcoxon rank-sum test and Student’s $t$-test, respectively. The correlation between improvements in IPSS was analyzed using logistic regression. A probit analysis was used to determine the minimum level to predict efficacy in a scattered diagram. The 95% confidence interval (CI) was calculated from the $t$ distribution as the mean estimated copy number ± $t$× standard error, where $t$ was estimated to be 2.042 from the Student’s $t$-table.

All tests were two-sided and $P$-values <0.05 were considered to be statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences for Windows (SPSS Inc, Chicago, IL, USA).

3. RESULTS

Sixty-four patients were excluded from the initial group of 196 patients, and the remaining 132 patients were included in the analysis. The reasons for exclusion were as follows: 49 patients did not satisfy the selection criteria (<50 or >80 years of age for two patients, IPSS <8 or QOL index <2 for 25, prostate volume <20 mL for eight, and $Q_{\text{max}}$ ≥ 15 mL/sec for 21), two did not adhere to the medication protocol, prostate volume was not available for two; and IPSS data were not available for 11.

Naftopidil treatment was observed to be efficacious (as defined by an improvement of total IPSS by five or more points) in 67 of the 132 patients (50.8%). Statistically significant differences were observed between responders ($n = 67$) and non-responders ($n = 65$) with regard to the baseline total IPSS and all IPSS items; these values were significantly higher in the responder group (Table 1). No significant differences were observed between these two groups in age or objective findings.

In all patients, there was a decrease in the mean total IPSS from 16.4 to 11.5, along with a significant improvement in the QOL index. $Q_{\text{max}}$, and all IPSS items after administration of naftopidil, while no improvement was observed in residual urine volume (Table 1). In the responder group, significant improvements were observed in total IPSS (from 19.6 to 9.8), QOL index, $Q_{\text{max}}$, residual urine volume, and all IPSS items after treatment. In contrast, in the non-responder group, no parameter except the QOL index improved significantly. The values of all subjective parameters were lower in the responders than in the non-responders after treatment (Table 1).

Multivariate analysis revealed a positive correlation between the efficacy rate and pretreatment total IPSS ($p < 0.001$). No significant correlation was noted between the efficacy rate and the patients’ age, prostate volume, $Q_{\text{max}}$, or residual urine volume. The symptoms among the IPSS parameters that demonstrated a strong correlation with the efficacy rate were weak stream (95% CI: 1.176–2.104, $P = 0.002$) and nocturia (95% CI: 1.312–3.026, $P = 0.001$); the symptom of straining showed a weak correlation with the efficacy rate (95% CI: 1.007–1.924, $P = 0.045$) (Table 2).

The correlation between weak stream and nocturia and the efficacy rate has been shown as a scattered diagram.
<table>
<thead>
<tr>
<th>TABLE 1. Patients' characteristics of responder and non-responder groups</th>
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<tbody>
<tr>
<td><strong>All patients</strong> Mean (standard deviation)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Prostate volume (mL)</strong></td>
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<tr>
<td><strong>IPSS total score</strong> Before administration</td>
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<td><strong>QoL index</strong> Before administration</td>
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<td><strong>Qmax (mL/sec)</strong> Before administration</td>
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<tr>
<td><strong>Residual urine volume (mL)</strong> Before administration</td>
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<tr>
<td>After 12 weeks</td>
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<tr>
<td><strong>IPSS item</strong> Feeling of in complete voiding Before administration</td>
</tr>
<tr>
<td>Frequency Before administration</td>
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<tr>
<td>Interruption of urinary stream Before administration</td>
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<tr>
<td>Urgency Before administration</td>
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<tr>
<td>Weak stream Before administration</td>
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<tr>
<td>Strained voiding Before administration</td>
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<tr>
<td>Nocturia Before administration</td>
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</table>

IPSS, international prostate symptom score; Qmax, maximum flow rate; QoL, quality of life.
Table 2. The correlation between pretreatment international prostate symptom score (IPSS) parameters and the efficacy rate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of incomplete voiding</td>
<td>0.679–1.290</td>
<td>0.687</td>
</tr>
<tr>
<td>Frequency</td>
<td>0.969–1.901</td>
<td>0.076</td>
</tr>
<tr>
<td>Interruption of urinary stream</td>
<td>0.957–1.697</td>
<td>0.097</td>
</tr>
<tr>
<td>Urgency</td>
<td>0.933–1.690</td>
<td>0.134</td>
</tr>
<tr>
<td>Weak stream</td>
<td>1.176–2.104</td>
<td>0.002</td>
</tr>
<tr>
<td>Strained voiding</td>
<td>1.007–1.924</td>
<td>0.045</td>
</tr>
<tr>
<td>Nocturia</td>
<td>1.312–3.026</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. 1. Scatter diagram demonstrating the relationship between the symptoms of weak stream and nocturia and the efficacy rate of naftopidil. The efficacy rates were demonstrated as effective cases/total cases. X axis: scores for the international prostate symptom score (IPSS) item of weak stream. Y axis: scores for IPSS item of nocturia. White column, an efficacy rate between 75 to 100%; bright gray column, efficacy rate ranging from 55 to 80%; and dark gray column, an efficacy rate less than 50%.

(If the score for weak stream was >4 and that for nocturia was >3, efficacy rates were shown to be high. This was also statistically confirmed by using probit analyses as described as follows; when the score for weak stream exceeded 4, the efficacy rate was expected to range from 70 to 80%. When the score for weak stream was <4, patients with a nocturia score ≥3 showed an efficacy rate ranging from 40 to 80%. Whereas, when the score for nocturia exceeded 3, all patients showed an efficacy rate ranging from 40 to 85%. When the score for nocturia was <3, patients with a score for weak stream ≥4 showed an efficacy rate ranging from 55 to 80%.)

4. DISCUSSION

Changes in subjective scoring and objective findings are usually used as parameters to assess therapeutic efficacy for patients with BPH/LUTS; however, those in an entire treatment group do not exactly reflect the drug efficacy in a clinical situation. Therefore, we applied the concept of an efficacy rate to assess the efficacy of naftopidil and to analyze the key symptoms that predict the response to treatment. Our study demonstrated that the total IPSS in the entire patient population ameliorated by 4.9 points after treatment, decreasing from 16.4 to 11.5. However, the change in IPSS was −9.8 points in the responder group and +0.1 points in the non-responder group when the patients were divided into two groups with a cut-off value of 5-point improvement in the total IPSS. Along with the results that the patients who were categorized as responders comprised 50.8% of all analyzed patients, acceptable improvement in subjective symptoms was achieved in about half of the patients following naftopidil administration. The results of our study showed that the total IPSS and most of the individual scores for the IPSS items were significantly higher in the responder group at baseline than in the non-responder group, and that the values of all of the evaluated parameters were lower in the responder group than in the non-responder after treatment. These results also meant our cut-off value was appropriate.

The IPSS system can be used as the voiding or storage symptoms separately not only as the total scores. Dividing the symptom-related items in the IPSS into these two categories was also proved to be valid psychometrically. We demonstrated that a score ≥3 for weak stream or ≥4 for nocturia was predictive for the efficacy of naftopidil treatment. These items are representative of the voiding and storage symptoms, respectively. It has been well recognized that among all LUTS, weak stream and nocturia are the symptoms that cause the most bother to patients. The present findings suggest that the severity of bother is a key parameter that predicts the efficacy of the drug treatment in BPH patients.

4. DISCUSSION

Our study has some limitations. First, although the present study was conducted as a prospective study, it...
was not a placebo-controlled, randomized study. The efficacy of naftopidil may not be conclusively determined on the basis of this study. We could not completely rule out placebo effect as the reason for the dissociation in the changes between subjective symptoms and objective findings. However, the new insights gained about predictive factors from this study may help in providing clinical benefits to patients with BPH/LUTS. Second, the period of the present study was rather short. In the retrospective study conducted by de la Rosette et al.\textsuperscript{25} on 316 BPH patients undergoing treatment with α1-AR antagonists for more than 3 years, a high total IPSS of ≥20 at baseline was suggested to be one of the risk factors associated with long-term treatment failure. Although our study demonstrated that a high score for weak stream or nocturia in the IPSS was predictive for a good response to naftopidil treatment over a short period, it is necessary to investigate whether this is also the case in long-term treatment.

**Acknowledgment**

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**Disclosure**

The authors have no conflict of interest to disclose.

**REFERENCES**