Cutoff level of prostate volume to predict the efficacy of α1-D/A adrenoceptor antagonist, naftopidil

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Abstract

Introduction: In lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) patients, prostate volume (PV) at baseline affects the improvement of International Prostate Symptom Score voiding symptoms (IPSS-VS) by naftopidil (NAF), but not total IPSS (IPSS-TS). To predict the efficacy of NAF, the PV cutoff point was examined using IPSS-VS.

Materials and Methods: Seventy-seven patients with LUTS/BPH were administrated with NAF 50 mg/day for 4 weeks. Age, PV, IPSS, IPSS quality-of-life (IPSS-QoL), and maximum flow rate (MFR) were evaluated at baseline, and IPSS, IPSS-QoL, and MFR were evaluated after the treatment (at 4 weeks). Responders and nonresponders were divided by IPSS-VS at 4 weeks, and the PV cutoff point was calculated.

Results: At baseline, the mean age and PV were 70.7 ± 8.2 years (range, 54–88 years) and 43.3 ± 24.5 mL (range, 20.6–141.7 mL), respectively. After 4 weeks, area under the receiver operating characteristic curve was largest in the patients with <4 points of IPSS-VS. The best standard value to evaluate the efficacy IPSS-VS at 4 weeks was 4 points for the NAF treatment, and the best PV cutoff point was 37.3 mL (sensitivity 60.5%, specificity 71.9%).

Conclusions: PV at baseline was one of the predictive factors which affected the efficacy of NAF for IPSS-VS, and LUTS/BPH patients who had PV more than 37.3 mL indicated poor improvement of IPSS-VS, even if IPSS-TS was improved.

Keywords: Benign prostatic hyperplasia, lower urinary tract symptom, naftopidil

INTRODUCTION

Prostate volume (PV) at baseline affected the long-term outcome with the treatment of α1-adrenoceptor antagonist (α1-blocker; α1-B) in lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) patients.[1-6] PV is seemed to be a predictive factor to affect the short-term efficacy of International Prostate Symptom Score voiding symptoms (IPSS-VS) in naftopidil (NAF) treatment (50 mg/day for 4 weeks).[7] However, the PV cutoff point, which can predict the short-term efficacy of IPSS-VS, is unknown in the NAF treatment.

Hence, we examined the PV cutoff point at baseline that could predict the efficacy of NAF using IPSS-VS.

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MATERIALS AND METHODS

The present study was conducted retrospectively, and 77 patients were enrolled by the hospital or clinic who participated in this study from July 2008 to February 2014, and all patients were given NAF 50 mg/day for 4 weeks. The inclusion criteria were the patients with a clinical diagnosis of LUTS/BPH together with age ≥50 years, PV ≥20 mL, total IPSS (IPSS-TS) ≥8, and IPSS quality-of-life (IPSS-QoL) ≥3. The following patients were excluded: prostatic cancer, bladder outlet obstruction (BOO), disease activity across multiple organs suspected serious conditions, comprehension difficulties, or serious conditions receiving α1-B for hypertension. Patients judged by the attending physician to be inappropriate were also excluded. Age and PV were evaluated at the start of treatment (baseline). IPSS, IPSS-QoL, voided volume (VV), maximum flow rate (MFR), and postvoid residual urine volume (PVR) were evaluated at baseline and 4 weeks.

For the statistical comparison between the baseline and 4 weeks, IPSS-TS, IPSS storage symptoms (IPSS-SS), IPSS-VS, and IPSS- QoL were analyzed using Wilcoxon signed-rank test, whereas VV, MFR and PVR were compared using paired t-test. The comparison between groups for PV, MFR and PVR were analyzed using Student's t-test, and others were done using Mann–Whitney U-test.

The correlation and regression of IPSS-VS at 4 weeks and change in IPSS-TS from the baseline to 4 weeks were analyzed using Spearman's rank correlation coefficient. For estimation of the PV cutoff point, the best standard value of IPSS-VS at 4 weeks was calculated using area under the receiver operating characteristic (ROC) curve. The sensitivity and specificity of PV cutoff point were evaluated using the ROC curve. The continuous values were summarized as mean ± standard deviation. All analyses were performed by SPSS version 22 (IBM Japan, Tokyo, Japan) with the two tailed, and $P < 0.05$ was considered statistical significance.

This study was approved by the institutional review board of Hokkaido Social Welfare Association Hakodate Hospital and obtained all participants' consent.

RESULTS

Of the 77 patients who were enrolled, six patients did not visit after 4 weeks and one patient was noncompliance. Accordingly, PV cutoff point was analyzed in a total of 70 patients. Baseline characteristics, change in subjective symptoms, and objective findings are shown in Table 1. Mean age and PV were 70.7 ± 8.2 years (range, 54–88 years) and 43.3 ± 24.5 mL (range, 20.6–141.7 mL), respectively.

IPSS-TS, IPSS-SS, IPSS-VS, and IPSS-QoL at 4 weeks were significantly improved as compared to the baseline; however, the changes of VV, MFR, and PVR were not statistical significance.

In the AUA guidelines, α1-Bs improve IPSS-TS by 4–6 points on an average.[8] Therefore, we presumed IPSS-VS at 4 weeks equivalent to the 4–6 points reduction in IPSS-TS from the baseline (ΔIPSS-TS). As shown in Table 2, IPSS-VS at 4 weeks and Δ IPSS-TS were significantly correlated ($\rho = 0.476$, $P < 0.001$). The regression equation is shown below:

IPSS-VS at 4 weeks = 0.2896 × ΔIPSS-TS + 6.2671.

At 4 weeks, IPSS-VS, which is equivalent to decrease of IPSS-TS (less than 4 points), was calculated according to the regression equation, and it was estimated to be less than 5.1 points.

Table 1: Baseline characteristics and changes in subjective symptoms and objective findings (*n*=70)

	Baseline	4 weeks	*P*
Age (years)	70.7±8.2	-	-
PV (mL)	43.3±24.5	-	-
Total IPSS (IPSS-TS)	16.5±5.8	11.8±6.6	<0.001
IPSS-SS	7.3±2.6	5.3±2.8	<0.001
IPSS-VS	6.9±4.3	4.9±3.9	0.001
IPSS-QoL	4.7±1.0	3.2±1.6	<0.001
VV (mL)	166.4±113.0	160.2±90.3	NS
MFR (mL/s)	12.0±7.3	13.4±7.7	NS
PVR (mL)	62.5±69.2	62.9±86.1	NS

Statistical analysis was performed with paired t-test (VV, MFR, and PVR) and Wilcoxon signed-rank test (for others). *P*<0.05 was considered as statistical significance. IPSS: International Prostate Symptom Score, SS: Storage symptoms score (frequency, urgency, and nocturia), VS: Voiding symptoms score (intermittency, weak stream, and straining), QoL: Quality of life, PV: Prostate volume, VV: Voided volume, MFR: Maximum flow rate, PVR: Postvoid residual urine volume, NS: Not significance

Table 2: International Prostate Symptom Score voiding symptoms at 4 weeks which was estimated by the equation

Change in ΔIPSS-TS	Estimated IPSS-VS at 4 weeks
−4	5.1
−5	4.8
−6	4.5
−7	4.2
−8	4.0
−9	3.7
Regression equation	IPSS-VS at 4 weeks=0.2896×(ΔIPSS-TS)+6.2671

ΔIPSS-TS: Change in IPSS-TS from the baseline to 4 weeks. IPSS: International Prostate Symptom Score, TS: Total score, VS: Voiding symptoms score (intermittency, weak stream, and straining)

As shown in Table 3, Area under the ROC curve (Az) was the largest in the patients with 4 points or less of IPSS-VS at 4 weeks. ROC curve was plotted to examine the PV cutoff point [Figure 1]. The PV cutoff point which evaluated the efficacy of NAF using IPSS-VS was 37.3 mL (sensitivity 60.5%, specificity 71.9%).

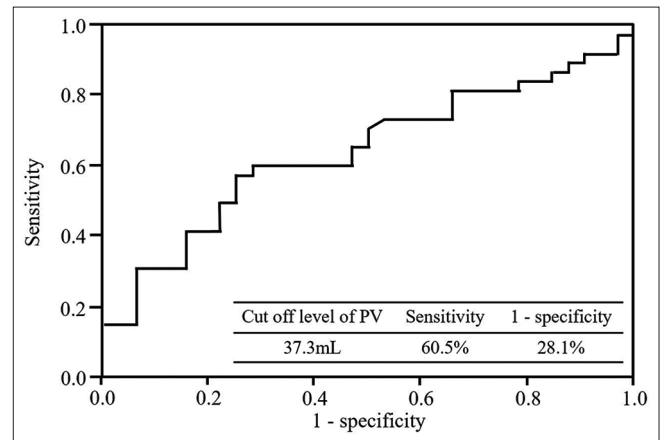In the patients who had >37.3 mL of PV (Group large) and <37.3 mL (Group small), the efficacy of NAF is shown in Table 4. All IPSS-TS, IPSS-SS, and IPSS-VS at 4 weeks were significantly improved compared with the baseline in the Group small, whereas in the Group large, only IPSS-TS and IPSS-SS were improved significantly.

DISCUSSION

In the previous investigations, PV at baseline affected the long-term outcome with the treatment of α1-B in LUTS/BPH patients.[1-5] The European Association of Urology guidelines show that pressure flow study is useful in the diagnosis of lower urinary tract (including bladder) functions. However, it is an invasive and serious burden for LUTS/BPH patients. If the prediction is not invasive in the efficacy, the procedure must be convenient for the patients. If a predictive factor of the efficacy is noninvasive, it must be convenient for the patients.

In the long-term pharmacotherapy, BOO often generates a treatment failure. Ultrasonography declared PV or intravesical prostatic protrusion (IPP) was the predictive factor of BOO.[5,9-13] According to a multivariate logistic regression analysis, IPP is a better predictive factor of BOO in comparison with PV,[10,11] whereas Kim *et al.* showed that PV was the most important independent noninvasive predictive factor of BOO, among PV, Qmax, and PVR.[12] Trumbeckas *et al.* showed that average/peak flow rate combined with PV could be used for the prediction of BOO.[13] Therefore, we thought that PV might be evaluated with one of predictive factors of BOO.

Conversely, it was reported that PV is negatively a predictive factor of the treatment failure in the short-term α1-B dosing.[6,14,15] However, IPSS-TS was improved by tamsulosin for 16 weeks in the patients with large PV as

Table 3: The best standard value to evaluate the efficacy of naftopidil by International Prostate Symptom Score-voiding symptoms at 4 weeks

IPSS-VS at 4 weeks for the effective case	Az	P	95% CI
≤6 points	0.622	NS (0.084)	0.486-0.758
≤5 points	0.623	NS (0.077)	0.490-0.755
≤4 points	0.646	0.036	0.516-0.776
≤3 points	0.536	NS (0.631)	0.398-0.674

IPSS: International Prostate Symptom Score, VS: Voiding symptoms (intermittency, weak stream, and straining), Az: Area under the receiver operating characteristic curve, CI: Confidence interval, NS: Not significance

Table 4: Subgroup analyses between stratified prostate volumes by the cutoff point in the receiver operating characteristic

Group (n)	Baseline	4 weeks	P
IPSS-TS			
Large (32)	16.8±6.3	13.1±7.5	0.018
Small (38)	16.2±5.4	10.7±5.6	<0.001
P	NS	NS	
IPSS-SS			
Large (32)	7.1±2.3	5.3±3.1	0.006
Small (38)	7.5±2.9	5.3±2.7	<0.001
P	NS	NS	
IPSS-VS			
Large (32)	7.3±4.3	6.3±4.3	NS
Small (38)	6.5±4.3	3.8±3.1	0.003
P	NS	0.014	
IPSS-QoL			
Large (32)	4.5±0.9	3.3±1.4	<0.001
Small (38)	5.0±1.0	3.2±1.8	<0.001
P	0.032	NS	
MFR (mL/s)			
Large (32)	11.3±5.7	12.9±6.8	NS
Small (38)	12.6±8.5	13.8±8.4	NS
P	NS	NS	
PVR (mL)			
Large (32)	73.8±70.8	81.1±109.8	NS
Small (38)	52.9±67.2	47.6±56.4	NS
P	NS	NS	

Group large and small mean the subgroups which are divided by PV≥ 37.3 mL and PV<37.3 mL, respectively. Statistical analysis between groups was performed with Student's *t*-test (MFR and PVR), and Mann-Whitney U-test (for others). Analysis within groups was compared using paired *t*-test or Wilcoxon signed-rank test. *P*<0.05 was considered as statistical significance. PV: Prostate volume, IPSS: International Prostate Symptom Score, TS: Total score, SS: Storage symptoms score (frequency, urgency, and nocturia), VS: Voiding symptoms score (intermittency, weak stream, and straining), QoL: Quality of life, MFR: Maximum flow rate, PVR: Postvoid residual urine volume, NS: Not significance

Cut off level of PV	Sensitivity	1 - specificity
37.3mL	60.5%	28.1%

Figure 1: Cutoff point of PV using ROC curve. ROC: Receiver operating characteristics, PV: Prostate volume

compared to those with small PV.[16] On the other hand, α1-B was effective in LUTS/BPH patients with the small PV superior to the large PV.[17-19] The discrepancy of these results can be explained that evaluations for outcomes were probably nonuniform among those investigations. Therefore, we assume that PV is considered as one of the predictive factors which affect the efficacy of α1-B at least.

It was reported that only the symptoms of hesitancy and poor flow were found to be significantly related to BOO.[20] Hence, regarding voiding symptoms, LUTS/BPH patients with small PV indicated improving IPSS-VS at 4 weeks compared with the patients with large PV in the NAF treatment, but IPSS-SS and IPSS-TS were the equal efficacy regardless of PV.[7]

In the present study, PV cutoff point was able to evaluate the efficacy of 4 weeks NAF 50 mg/day treatment using IPSS-VS. As the result, IPSS-VS at 4 weeks can potentially evaluate improvement of subjective symptoms, because IPSS-VS at 4 weeks and Δ IPSS-TS were significantly correlated, and the best PV cutoff point was 37.3 mL when the patients with less than 4 points of IPSS-VS at 4 weeks were defined as effective.

However, the significantly PV cutoff point was not able to find when IPSS-TS or IPSS-SS was used as a parameter of the efficacy (data not shown). The patients with less than 37.3 mL of PV significantly improved IPSS-VS at 4 weeks in comparison with the patients who had more than 37.3 mL, whereas improvement of IPSS-TS and IPSS-SS was similar in both subgroups. Therefore, the PV cutoff point of 37.3 mL is likely appropriate in the present study. These results are supported by the previous investigation by Hong *et al.*, who showed that predictive factors which affect the efficacy of the therapy were PV and IPSS at baseline, and the best cutoff point of the PV and IPSS was 35.65 mL and 23.5 points, respectively.[17] Moreover, in the previous studies in the different groups, the values of PV of the nonresponders by naftopidil treatment were 35.1 and 36.7 mL, respectively.[18,19]

In the present study, there were several limitations that the cutoff point of IPP was not presented. The statistical analyses were *post hoc* analysis and small sample size. Therefore, the prospective study on the predictive factors in short-term efficacy of α1-B treatment is needed, particularly using easy measurement and subjective symptoms.

CONCLUSION

IPSS-VS at 4 weeks is able to evaluate the improvement of

subjective symptoms. Moreover, in the patients with more than 37.3 mL of the baseline PV, the voiding symptoms were likely to poor improvement even if subjective symptoms were significantly improved. These results are informative to reconsider the treatment strategy in LUTS/BPH patients who were given NAF for 4 weeks.

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Conflicts of interest
There are no conflicts of interest.

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