Prostate Int 4 (2016) 30–35

Contents lists available at ScienceDirect

Prostate International

journal homepage: http://p-international.com

Original Article

The prostatic urethral angle can predict the response to alpha adrenoceptor antagonist monotherapy for treating nocturia in men with lower urinary tract symptom: A multicenter study

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ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form
28 December 2015
Accepted 30 December 2015
Available online 14 January 2016

Keywords:
Adrenergic alpha-antagonists
Benign prostatic hyperplasia
Nocturia
Prostate

ABSTRACT

Background: We evaluated ultrasonography variables associated with the improvement of nocturia after administration of alpha adrenoceptor antagonist (alpha blocker) monotherapy.

Methods: From February to October 2014, 679 men with lower urinary tract symptoms (LUTS) underwent ultrasonography including prostate volume, transitional zone volume, prostatic urethral length, the ratio between prostatic urethral length and prostate volume (RPUL), intravesical prostatic protrusion (IPP), and prostatic urethral angle (PUA). Among them, 108 men who had pre-treatment nocturia without nocturnal polyuria (nocturnal polyuria index < 33%) and were treated with alpha blocker monotherapy over 3 months were enrolled. Patients were divided into the improved (< 2 times of nocturia) and non-improved group (more than 2 times) after administration of alpha blockers. Along with ultrasonography, international prostate symptom score (IPSS) and uroflowmetry was assessed.

Results: After alpha blocker treatment, 25.0% of patients (27/108) showed improvement of nocturia. These patients were significantly younger (59.6 vs 68.0 years, $P = < 0.001$) with lower PUA (31.8 vs. 39.4°, $P = 0.009$) compared with the non-improved group. In ROC analysis, the area under the curve using the PUA was 0.653 (95% CI = 0.532–0.774, $P = 0.018$). Using 33.5° as a cut-off level, the sensitivity and specificity for predicting the improvement of nocturia after medication reached 67.9% and 55.6%, respectively. Patients with lower PUA (PUA < 33.5°) had more improvement of nocturia (36.6 vs. 17.9%, $P = 0.030$), lower IPSS score (14.2 vs. 18.3, $P = 0.005$), and better quality of life index (3.1 vs 3.8, $P = 0.021$).

Conclusions: In the patients with lower PUA (particularly lower than 33.5°), nocturia was improved by administration of alpha blocker monotherapy.

1. Introduction

Nocturia, which is usually included as a lower urinary tract symptom (LUTS), is a common cause of an adult sleep disorder (e.g., obstructive sleep apnea, enuresis). A recent meta-analysis suggests that the prevalence rate of nocturia was 11–43.9% in younger persons (i.e., 20–40 years) and 68.9–93% in older persons (i.e., > 70 years).[1] Nocturia is not a simple LUTS; it is a multifactorial condition with many contributing etiological factors. It has four major underlying causes: global polyuria, nocturnal polyuria, bladder storage disorders, or mixed etiology.[2] Nocturia is often associated with men with benign prostatic hyperplasia (BPH).[3] The effect of an alpha adrenoceptor antagonist (i.e., an alpha blocker) on nocturia was demonstrated in patients with BPH. It may reduce residual urine and thus increase the room for nocturnal urine storage.[4] However, the improvement in nocturia is clinically marginal, poorly sustained, and depends on the patients.[5]

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http://dx.doi.org/10.1016/j.prnil.2015.12.002

We hypothesized that individual differences in the effect of an alpha blocker can be attributed to structural differences of the prostate. To provide an integral description of individual differences in the prostate, we evaluated ultrasonography variables associated with the improvement of nocturia after the administration of alpha blocker monotherapy.

2. Materials and methods

2.1. Patient enrollment

This multicenter cross-sectional study was conducted using the same protocol in five tertiary care hospitals in the Daegu area (Dongguk University Kyeongju Hospital, Keimyung University Dongsan Medical Center, Kyungpook National University Hospital, Kyungpook National University Medical Center, Yeungnam University Medical Center, Daegu, Korea), after the approval of the local Institutional Review Board (approval number, 13-0496-O82). Six hundred and seventy-nine men were examined from February 2014 to October 2014. Of these, 108 men were included in this study who had pretreatment nocturia (defined as $\geq$ 2 awakenings at night to void) and were treated with alpha blockers monotherapy (i.e., tamsulocin, doxazocin, alfuzocin, terazocin, naftopidil, or silodocin) for > 3 months (average, 11.5 months; range, 3–102 months). However, patients with nocturnal polyuria (i.e., nocturnal polyuria index > 33%) were excluded from this study. Other exclusion criteria were as follows: presence of an indwelling urinary catheter, previous prostate surgery or pelvic radiation, urethral stricture, inflammation of urinary tract, prostate or bladder cancer, and neurogenic bladder disease. Patients were divided by the improved group (i.e., < 2 episodes of nocturia) and the non-improved group (i.e., $\geq$ 2 episodes of nocturia) after the administration of alpha blockers.

2.2. Parameter measurements

Detailed previous medical history, particularly BPH medication (e.g., use of alpha blockers, 5-α reductase inhibitors (5ARIS), phosphodiesterase inhibitors, antimuscarinic agents, and desmopressin) at the time of evaluation and previous admission or BPH-related surgical history was obtained from all enrolled patients. We reviewed the degree of LUTS at pretreatment by using clinical records of the international prostate symptom score (IPSS) and voiding diary. At post-treatment, routine subjective assessment of the degree of LUTS was performed using the IPSS and voiding diary, and objective assessment was performed using uroflowmetry and transrectal ultrasonography examination. Along with total IPSS, scores divided according to obstructive symptoms (Questionnaires 1, 3, 5, and 6), irritative symptoms (Questionnaires 2, 4, and 7), and quality of life (Questionnaire 8) were also utilized as a separate clinical indicator. Bothersome voiding symptoms, particularly the presence of nocturia were also evaluated. After treatment with alpha blocker monotherapy, uroflowmetry was performed in the usual manner. The amount of post-voiding residual urine was measured using ultrasonography. Patients also underwent transrectal ultrasonography (TRUS) for the evaluation of LUTS at post-treatment. During TRUS, the prostate volume, transitional zone volume, prostatic urethral length, the ratio between prostatic urethral length and prostate volume (RPUL), intravesical prostatic protrusion (IPP), and prostatic urethral angle (PUA) were determined during a single session. The prostate and transitional zone volume were measured by calculating the maximal height, width, and length on ultrasonography (i.e., 0.52 $\times$ transverse diameter $\times$ anteroposterior diameter $\times$ cephalocaudal diameter). The prostatic urethral length was measured by the continuous tracing of the route of the urethra, which runs within the apex to the base of the prostate via the midsagittal image of ultrasonography. The measured prostatic urethral length was then utilized to describe the individual morphologic variation of the prostate [i.e., RPUL (mm/mL)]. The IPP was measured by TRUS when the bladder volume was 100–200 mL. The degree of IPP was graded by measuring from the tip of the protruding gland perpendicular to the bladder circumference at the prostate base in the midsagittal plane. The PUA is the angle formed by two rays of the proximal and distal prostatic urethra on the midsagittal plane image, and was taken with the posterior wall of the prostate positioned as flat as possible to minimize the influence of pressure from the rectal probe (Fig. 1).

2.3. Data and statistical analysis

The correlation between the improvement in nocturia after alpha blocker monotherapy and clinical parameters such as age, prostate-specific antigen (PSA), post-treatment IPSS, post-treatment uroflowmetry, and post-treatment ultrasonography variables were analyzed. Patients were divided into two groups, according to improvement in nocturia after the administration of alpha blockers. Differences in parameters between groups were assessed using the Mann–Whitney *U* test. A receiver operating characteristic (ROC) curve was drawn and the sensitivity and

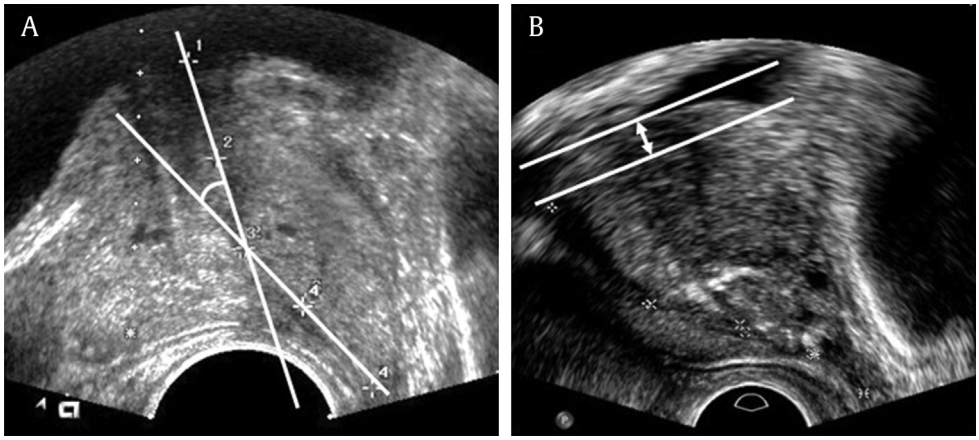

Fig. 1. Ultrasonographic measurement of prostatic urethral angle and Intravesical prostatic protrusion. (A) The prostatic urethral angle measured on the ultrasound image. (B) Intravesical prostatic protrusion measured on the ultrasound image.

Table 1
Clinical parameters based on the improvement in nocturia after the use of alpha blockers.

	Nonimproved group ($n = 81$)	Improved group ($n = 27$)	P
Age (y)	68.0 ± 9.4	59.6 ± 9.9	< 0.001
Prostate-specific antigen (ng/mL)	1.8 ± 2.1	2.2 ± 2.7	0.416
Transrectal ultrasonography			
Total prostate volume (mL)	29.8 ± 15.4	33.1 ± 18.1	0.368
Transition zone volume (mL)	13.4 ± 12.2	14.0 ± 13.4	0.831
Urethral length (cm)	4.0 ± 0.6	4.0 ± 0.7	0.764
RPUL (mm/mL)	1.5 ± 0.5	1.4 ± 0.4	0.102
PUA (°)	39.4 ± 12.6	31.8 ± 12.3	0.009
IPP (cm)	0.17 ± 0.4	0.21 ± 0.5	0.665
Post-treatment international prostate symptom score			
Total score	17.9 ± 7.9	13.4 ± 5.2	0.008
Voiding symptom score	10.5 ± 5.7	9.0 ± 4.0	0.133
Storage symptom score	7.4 ± 3.3	4.5 ± 2.2	< 0.001
Quality of life index	3.7 ± 1.4	3.0 ± 1.4	0.030
Post-treatment uroflowmetry			
Qmax. (mL/s)	11.9 ± 6.5	16.9 ± 6.6	0.002
Voiding volume (mL)	205.8 ± 126.8	254.5 ± 185.1	0.129
Postvoid residual volume (mL)	45.4 ± 54.7	30.3 ± 42.6	0.195

IPP, intravesical prostatic protrusion; PUA, prostatic urethral angle; Qmax, maximum flow rate; RPUL, the ratio between prostatic urethral length and prostate volume.

specificity of the different cut-off points for PUA were determined. The best cut-off point was chosen according to the ROC curve. The area under the curve was also calculated. The results were expressed with a 95% confidence interval (CI). Univariate and multivariate analyses performed to determine the improvement in nocturia were assessed using logistic regression analysis. Statistical analysis was performed using SPSS 21.0 for Windows software (SPSS Inc., Chicago, IL, USA). The significance level for all analyses was set at $P < 0.05$.

3. Results

After alpha blocker monotherapy treatment, 25.0% (27/108) of patients showed improvement in nocturia. In comparison with the nonimproved group, these patients were significantly younger (59.6 years vs. 68.0 years, $P \leq 0.001$) with a lower IPSS (13.4 vs. 17.9, $P = 0.008$), lower storage symptom score (4.5 vs. 7.4, $P \leq 0.001$), better quality of life index (3.0 vs. 3.7, $P = 0.030$), and higher maximum flow rate (Qmax; 16.9 mL/s vs. 11.9 mL/s; $P = 0.002$) at post-treatment. On TRUS, the nocturia group had a lower PUA (31.8° vs. 39.4°, $P = 0.009$; Table 1).

In univariate logistic analysis, age and the PUA were significantly associated with presence of nocturia ($P \leq 0.001$ and $P \leq 0.010$, respectively). In multivariate analysis, age and the PUA were also significantly associated with nocturia ($P = 0.001$ and $P = 0.021$, respectively; Table 2).

In ROC analysis, the area under the curve using the PUA was 0.653 [95% CI, 0.532–0.774; $P = 0.018$; Fig. 2]. Using 33.5° as the cut-off level, the sensitivity and specificity for predicting the improvement of nocturia after medication reached 67.9% and 55.6%, respectively.

Patients with lower PUA (i.e., < 33.5°) had more improvement in nocturia [36.6% vs. 17.9%, $P = 0.030$], compared to patients with a higher PUA (i.e., ≥ 33.5°). On the post-treatment IPSS, patients with a lower PUA had a lower total IPSS score (14.2 vs. 18.3, $P = 0.005$), lower voiding symptom score (8.6 vs. 11.0, $P = 0.025$), lower storage symptom score (5.6 vs. 7.3, $P = 0.006$), and better quality of life index (3.1 vs. 3.8, $P = 0.021$) (Table 3).

4. Discussion

Nocturia (i.e., nocturnal waking to void) occurs in up to 58.90% of people older than 50 years.[6,7] Its prevalence increases with age.[8,9] This condition can significantly impair a patient's perception of his or her well-being.[10,11] The International Continence Society definition of nocturia is a complaint of having to awaken once or more at night to void.[2] However, the traditional definition of nocturia is a complaint of having to awaken twice or more at night to void. In a cross-sectional, community-based epidemiologic survey conducted in Korea, the mean number of nocturia episodes was 2.05 times for men with BPH and 1.04 times for men without BPH.[12] Many studies on nocturia only consider patients with two or more voids per night, based on the observation that a nocturnal frequency of one void per night does not appear to be harmful or bothersome.[13,14] Therefore, in this study, nocturia was defined as awakening twice during sleep to void.

The etiology of nocturia recently included four major underlying causes: global polyuria, nocturnal polyuria, bladder storage

Table 2
Logistic regression analysis used to determine the factors that predict improvement in nocturia.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age (y)	1.095 (1.041–1.095)	< 0.001	1.094 (1.035–1.155)	0.001
Transrectal ultrasonography				
Total prostate volume (mL)	0.989 (0.964–1.014)	0.372	0.999 (0.882–1.132)	0.989
Transition zone volume (mL)	0.996 (0.963–1.031)	0.829	1.019 (0.902–1.152)	0.762
Urethral length (cm)	1.116 (0.567–2.197)	0.750	0.889 (0.218–3.632)	0.870
RPUL (mm/mL)	2.348 (0.839–6.576)	0.287	3.955 (0.419–37.343)	0.230
PUA (°)	1.055 (1.013–1.099)	0.010	1.059 (1.008–1.111)	0.021
IPP (cm)	0.784 (0.263–2.334)	0.662	0.674 (0.159–2.860)	0.593

CI, confidence interval; IPP, intravesical prostatic protrusion; PUA, prostatic urethral angle; RPUL, the ratio between prostatic urethral length and prostate volume.

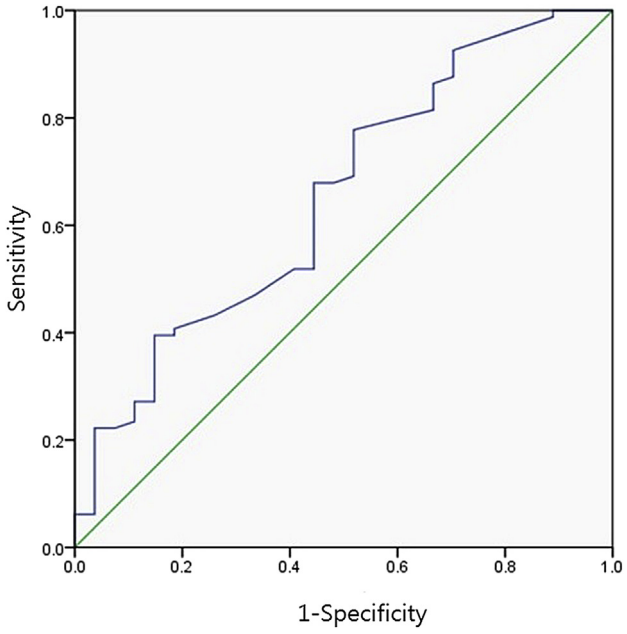

Fig. 2. The graph shows the receiver operating characteristic curves for prostatic urethral angle (AUC = 0.653, $P = 0.018$). AUC, area under the curve.

disorders, or mixed etiology. Men with benign prostatic enlargement (BPE) often have nocturia and nocturnal polyuria.[3] Benign prostatic enlargement leading to bladder outlet obstruction (BOO) clearly results in the obstructive type of voiding symptoms which comprises poor flow, hesitancy, prolonged stream, and terminal dribbling. In addition, storage symptoms are common in males in these age groups. However, as demonstrated in a cohort of 324 trial participants, urological problems were the only cause of nocturia in just 16% of patients.[15] Patients with nocturia who do not have polyuria or nocturnal polyuria based on the aforementioned criteria will most likely have a bladder storage disorder that reduces their nighttime voided volume or a sleep disorder.[16]

One of the most pertinent aspects of the relationship between nocturia and BPE is whether successful treatment of BPE resolves nocturia. Margel et al[17] report that nocturia appears to improve after transurethral resection of the prostate. Medical treatment with alpha blockers could similarly be indicated for male patients with nocturia when BPE is suspected. In a study[17] with terazosin, 27% of patients reported that nocturia was reduced by more than half, and 14% reported that it was reduced by 25–49% on the frequency-volume chart. On the IPSS, 31% of patients reported that the treatment reduced their nocturia by more than half and 27% reported a reduction of 25–49%.[18] However, in another trial,[19,20] the clinical significance of alpha blockers was doubted because the difference in nocturia episodes was too small between patients receiving treatment with alpha blockers and a placebo. A study with alfuzosin also reported a numerical improvement of −1.1 voids per night versus −0.8 with placebo ($P = 0.04$).[19] In the Veterans Administration Cooperative Study, nocturia decreased from a baseline mean of 2.5 episodes to 1.8 episodes, 2.1 episodes, 2.0 episodes, and 2.1 episodes in the terazosin group, finasteride, combination group, and placebo group, respectively.[20]

Table 3
Clinical parameters based on a prostatic urethral angle of 33.5°.

	PUA < 33.5° ($n = 41$)	PUA ≥ 33.5° ($n = 67$)	*P*
Improvement in nocturia (%)	36.6	17.9	0.030
Age (y)	63.8 ± 11.0	67.2 ± 9.6	0.094
Prostate-specific antigen (ng/mL)	1.6 ± 2.0	2.2 ± 2.3	0.167
Transrectal ultrasonography			
Total prostate volume (mL)	29.8 ± 15.4	31.2 ± 16.6	0.667
Transition zone volume (mL)	12.7 ± 12.5	14.0 ± 12.5	0.599
Urethral length (cm)	3.8 ± 0.5	4.1 ± 0.7	0.004
IPP (cm)	0.1 ± 0.3	0.2 ± 0.4	0.082
Post-treatment international prostate symptom score			
Total score	14.2 ± 7.6	18.3 ± 7.1	0.005
Voiding symptom score	8.6 ± 5.4	11.0 ± 5.2	0.025
Storage symptom score	5.6 ± 3.2	7.3 ± 3.1	0.006
Quality of life index	3.1 ± 1.5	3.8 ± 1.3	0.021
Post-treatment uroflowmetry			
Qmax. (mL/s)	14.1 ± 6.1	12.6 ± 7.2	0.296
Voiding volume (mL)	223.1 ± 146.4	214.9 ± 143.8	0.776
Postvoid residual volume (mL)	31.4 ± 45.6	47.9 ± 55.2	0.111

PUA, prostatic urethral angle; Qmax, maximum flow rate.

With regard to the medical treatment of BPH, 5ARI (e.g., dutasteride and finasteride) effectively reduced the prostate volume.[21] However, alpha blockers provide rapid relief of LUTS, presumably by relaxing the smooth muscle tone in the prostate and bladder neck.[22] In addition, the effect of alpha blockers on the structure of the prostate remains unknown. In our study, we did not have pretreatment TRUS data.

However, we believed that alpha blocker monotherapy would not change the structure of the prostate. We also hypothesized that structural features of the prostate could predict improvement in nocturia after alpha blocker monotherapy. Therefore, we investigated ultrasonography variables to provide an integral description of the individual structural differences of the prostate. As a result of this study, the PUA was the only structural variable that could predict improvement of nocturia after treatment by alpha blockers.

The PUA is a well-known structural feature of the prostate. In a study by Ku et al,[23] higher PSA levels, larger prostate volume, higher maximal urethral closure pressure, higher detrusor pressure at maximum flow rate, and higher BOO index were reported with a larger PUA. Using multivariate analysis, Bang et al[24] reported that PUA has an independent association with the IPSS. Hou et al[25] reported a change in symptoms after treatment with alpha blocker. In this study, the PUA had an independent association with the IPSS ($P = 0.001$) and Qmax ($P = 0.004$). After tamsulosin therapy, the PUA was associated with post-treatment IPSS change ($P = 0.032$) and post-treatment Qmax change ($P = 0.001$).

However, the relationship between the PUA and nocturia has not been reported. In the current study, patients with improved nocturia were significantly younger and had a lower PUA.

Age is a well-known factor in progression of nocturia.[3] The incidence and prevalence of nocturia showed a clear increase with age. Häkkinen et al[26] estimated the incidence and natural course of nocturia in an unselected Finnish male population. Every year, 10% more males older than 50 years start to void during the night. The incidence of mild nocturia increases, particularly in men aged 50–60 years. Older men with mild symptoms are more stable, but the incidence of severe nocturia increases significantly after the age of 75 years. Thus, in younger patients, a higher improvement rate of nocturia after alpha blocker monotherapy is very reasonable.

However, the relationship between the PUA and nocturia is meaningful. The value of the PUA is also confirmed by univariate analysis and multivariate analysis. In this report, we used a PUA of 33.5° as the cut-off level. We then determined that patients with a lower PUA had lower incidences of nocturia, lower total IPSS score, and better quality of life index. The cut-off level was slightly different according to the paper[23,27] (34°–35°); however, a lower PUA has generally been associated with improvement in symptoms and quality of life.[23,27] In this report, a lower PUA was also associated with an improvement in nocturia. In our opinion, a lower PUA

indicates that the urethra is straighter. Relaxing smooth muscle tone by alpha blockers provides more rapid relief of LUTS in a straight urethra. Therefore, it seems that nocturia also improved more in patients with a straight urethra.

In this study, we attempted to find other ultrasonography variables for predicting improvement of nocturia after alpha blocker monotherapy. Benign prostatic enlargement, which is a well-recognized feature of male aging, is commonly associated with LUTS. However, opinions are divided on whether prostatic enlargement has a causal relationship with storage symptoms such as nocturia.[28] In this paper, the total prostate volume and transition zone volume did not show a statistical difference between the improved group and the nonimproved group ($P = 0.368$ and $P = 0.831$, respectively). The RPUL is the relationship between the whole prostate and the prostate urethra. There are multitudinous patterns that consequently produce distinctive structural variation. The structural variation of the prostatic urethra within the prostate, as reflected by the ratio between prostate volume and prostatic urethral length, showed a correlation with the degree of LUTS.[29] We believe that the change in the urethra within the prostate due to the enlargement of the gland—instead of the prostate volume itself—may cause the development of nocturia. However no statistical difference was observed between the two groups ($P = 0.102$).

Intravesical prostatic protrusion is a useful predictor of infravesical obstruction, Qmax, acute urinary retention, and the outcomes of a trial without a catheter after acute urinary retention.[30–32] In our study, IPP also showed no statistical difference between the improved group and the nonimproved group ($P = 0.665$).

The authors recognize several limitations of this series. First, this trial was a multicenter prospective study conducted in five clinics. We tried to minimize deviation, although there was some technical difficulty. Second, many kinds of alpha blockers were used in this trial. A few recent studies reporting the effect of a selective alpha-1D blocker, naftopidil, on nocturia concluded that naftopidil was better than tamsulosin for treating nocturia.[33] However, differences between alpha blockers were not reflected in this study. Third, we only investigated patients who had nocturia without a decrease in the number of episodes after alpha blocker monotherapy. Fourth, most importantly, we did not report the change in TRUS findings before and after treatment. Further trials with a proper study design will be required to overcome these limitations and to obtain a solid answer for nocturia and anatomical variations of the prostate.

In patients who had a lower PUA (particularly lower than 33.5°), nocturia was improved by administration of alpha blocker monotherapy. These findings suggest an individualized approach in the treatment of nocturia, based on anatomical characteristics illustrated by ultrasonography.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

This study was supported by research fund from the Hannam Urological Association (Seoul, Korea) in 2014.

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