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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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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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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

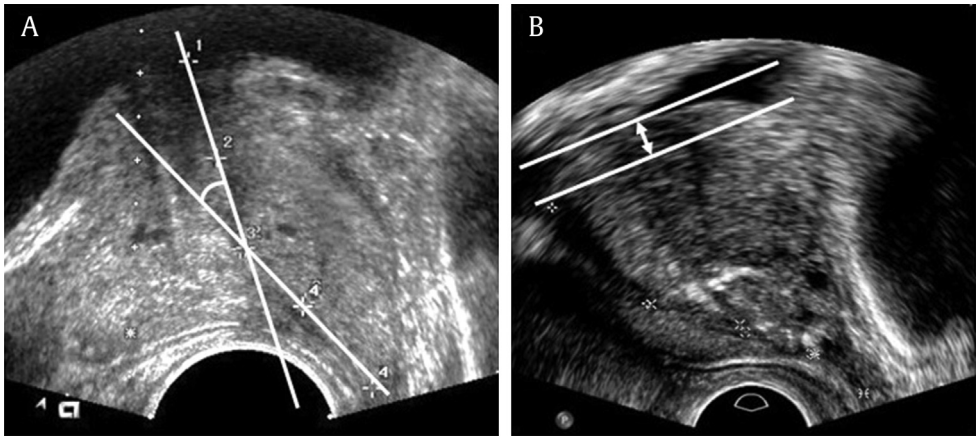

Fig. 1. Ultrasonographic measurement of prostatic urethral angle and Intravesical prostatic protrusion. (A) The prostatic urethral angle measured on the ultrasound image. (B) Intravesical prostatic protrusion measured on the ultrasound image.