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TAMSULOSIN IMPROVES DISTURBANCE OF CIRCADIAN REGULATION OF URINE PRODUCTION IN BENIGN PROSTATIC HYPERPLASIA PATIENTS WITH NOCTURNAL POLYURIA – A PROSPECTIVE OPEN-LABEL LONG-TERM STUDY USING FREQUENCY-VOLUME CHART

Hypothesis / aims of study

Nocturia is a common reason for interrupted sleep in the adult population, and the incidence increases markedly with age. Nocturia has a negative impact on quality of life (QOL), affecting both morbidity and mortality. The etiology of nocturia differs from that of other LUTS and is multifactorial, resulting from a broad range of urological and non-urological conditions. Although nocturnal polyuria (NP), reduced bladder capacity, and sleep disorders are considered to be causes of nocturia, nocturnal urine production has been implied as one of the main determining factors of nocturia in elderly men. NP is defined as nocturnal urine volume that constitutes more than 33% of total output (day-time plus night-time urine volume) in the elderly. Disturbance of the circadian regulation of urine production may induce NP. Circadian variation of plasma vasopressin is absent in elderly men, which is the main causative factor of NP; therefore, most attention has focused on the use of desmopressin acetate for patients with NP.

On the other hand, in patients with BPH, alpha$_1$-AR antagonists have produced modest improvement in nocturia; however, its mechanism remains unknown. In addition, to our knowledge, there is no report on the long-term evaluation of nocturia by alpha $_1$-AR antagonist administration using a frequency-volume chart (FVC). In this study, we performed a prospective study to evaluate the long-term effectiveness of tamsulosin using FVC, and discussed the mechanism of the improvement of nocturia in BPH patients, especially those with NP.

Study design, materials and methods

We enrolled 104 patients with LUTS secondary to untreated BPH diagnosed in the BPH outpatient clinic from 2002 to 2008. BPH was diagnosed on the basis of the International Prostate Symptom Score (IPSS), QOL index, ultrasonography, uroflowmetry and prostate needle biopsy. The inclusion criteria were BPH patients with IPSS >7, maximum flow rate by uroflowmetery (MFR) <15ml/s, and prostate volume (PV) >20ml. At the first visit, patients were screened for study eligibility on the basis of a complete medical and medication history, a detailed history of urinary symptoms using IPSS, previous treatments and/or surgery, complete physical examination, laboratory examination including prostate-specific antigen (PSA) and ultrasonography. At the second visit (usually 1 week after the first), we evaluated IPSS, QOL index, uroflowmetry and PSA to evaluate for study eligibility, as described above. After enrollment in the study, the patients were treated with tamsulosin 0.2mg once daily after breakfast. The standard doses of this drug that are commonly used in clinical practice in Japan were chosen.

Visit were scheduled every 4 weeks until week 12 (month 3) after study entry, and then every 12 weeks subsequently. All patients completed the IPSS, QOL index and 3-day frequency volume chart (FVC), and underwent uroflowmetry at enrollment and every visit after pharmacologic treatment with tamsulosin. If the patients forgot to complete 3-day FVC or failed to undergo uroflowmetry on the visit day, they were asked to visit the outpatient clinic again within 7 days. The primary endpoint was 24 months after tamsulosin treatment, after which patients continued to receive tamsulosin monotherapy, and the secondary endpoint was 48 months after treatment. Finally, only patients receiving tamsulosin for over 24 months were evaluated in this study.

Results

Finally, 82 patients (mean age: 70.9 ± 7.1, mean prostate volume: 35.6 ± 16.0 ml) were analyzed at the primary endopoint (Tables 1 and 2). Fifty-three patients received tamsulosin until the secondary endpoint.

On the basis of the FVC outcome, the patients were divided into two groups; NP (n=58) and non-NP (n=24). The IPSS, QOL index and MFR improved most months after treatment in both groups. IPSS nocturia score was also improved approximately 3 years after treatment in both groups. Mean day-time urine frequency was significantly decreased only 42 months after treatment in the NP group; on the other hand, it was decreased 1, 3, 15, 24, 27, 33 months after treatment in the non-NP group. A change in day-time urine frequency from the baseline in the non-NP group was larger than in the NP group 1, 12, 15, 21, 24, 27, 30, 33, 39 months after treatment. Mean night-time urine frequency on FVC was significantly decreased for 48 months in the NP group ($p<0.01$), while it was decreased only 1, 9, 12, 15, 18, 33, 36, 39 and 42 months after treatment in the non-NP group. There was no significant difference in the change in night-time urine frequency between groups. Mean daytime urine volume was significantly increased in the NP group most months after treatment, while this was hardly found in the non-NP group. A change in daytime urine volume from the baseline in the NP group was significantly larger than in the non-NP group most months after treatment. A significant decrease was found in the night-time urine volume of the NP group for 48 months, although this decrease was not found in the non-NP group. The change in night-time urine volume in the NP group from the baseline was significantly larger than in the non-NP group most months after treatment. A significant change in the 24-hour urine volume was not found after treatment in either group. Maximum voided volume was increased most months after treatment in both groups. A change in maximum voided volume from the baseline in the non-NP group was significantly larger than in the NP group 6, 12, 15, 21, 24, 39 and 45 months after treatment.

Interpretation of results

The IPSS, QOL index and MFR improved for 48 months after treatment in NP and non-NP groups. Interestingly, however, not only a significant decrease in the night-time urine volume but also a significant increase in the daytime urine volume was found for 48 months in the NP group, although these changes were not found in the non-NP group.

Concluding message

Our long-term prospective study using FVC demonstrated that tamsulosin improves disturbance of the circadian regulation of urine production in BPH patients with NP. On the other hand, other medical options may be needed for BPH patients without NP to improve nocturia, because other responsible factors, which induce bladder dysfunction, night-time urine production or sleep disturbance, may mainly contribute to nocturia. FVC is a useful tool to not only evaluate each patient's characteristics and the effectiveness of medical therapy but also to identify the most efficient and personalized therapy for each BPH patient.

Specify source of funding or grant	**None**
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Is this study registered in a public clinical trials registry?	**No**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Nagoya City University Ethics Committee**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**