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Tamsulosin Reduces Nighttime Urine Production in Benign Prostatic Hyperplasia Patients With Nocturnal Polyuria: A Prospective Open-Label Long-Term Study Using Frequency–Volume Chart

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Aims: The effects of tamsulosin treatment on changes in frequency–volume chart (FVC) data, especially nighttime urine production, over time were assessed, and the mechanisms underlying the improvement of nocturia in benign prostatic hyperplasia (BPH) patients with nocturnal polyuria (NP) are discussed. **Methods:** A total of 104 patients with lower urinary tract symptoms secondary to BPH were enrolled. After enrollment in the study, the patients were treated with tamsulosin (0.2 mg) once daily. Visits were scheduled every 4 weeks until week 12 (month 3) after study entry, and then every 12 weeks subsequently. All patients completed the International Prostate Symptom Score (IPSS), quality of life (QOL) index, and 3-day FVC, and underwent uroflowmetry at enrollment and on each visit. **Results:** Eighty-two patients (mean age: 70.9 ± 7.1 years) were analyzed for 24 months after treatment. Patients were divided into two groups, NP and nonNP, based on FVC outcome. The IPSS, QOL index, and maximum flow rate improved during the 24-month period after treatment in both groups. Mean daytime urine volume significantly increased in the NP group, but no changes were detected in the nonNP group. Mean nighttime urine frequency significantly decreased in the NP group over a 24-month period, and was associated with a significant decrease in nighttime urine volume that was not found in the nonNP group. Maximum voided volume increased most months after treatment in both groups. **Conclusions:** The present long-term prospective study using FVC demonstrated that tamsulosin reduced nighttime urine production in BPH patients with NP. *Neurourol. Urodynam. 31:80–85, 2012.*

Key words: α1-AR antagonist; benign prostatic hyperplasia; long-term; nocturia; nocturnal polyuria

INTRODUCTION

The use of alpha1-adrenoceptor (α_1-AR) antagonists is the most frequent therapeutic approach for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) and is the first-line treatment for LUT/BPH. The subtype-selective α_1-AR antagonist tamsulosin significantly improved not only voiding symptoms but also storage symptoms, including nocturia, similar to other α_1-AR antagonists in randomized studies.[1–3] Although the use of these antagonists has been demonstrated to be effective as a short-term treatment option, controlled long-term efficacy data are not widely available.[4]

Nocturia is a common reason for interrupted sleep in adults, and its incidence increases markedly with age. Nocturia has a negative impact on the quality of life (QOL), affecting both morbidity and mortality.[5] The etiology of nocturia differs from that of other LUTS[6] and is multifactorial, resulting from a broad range of urological, and nonurological conditions.[7] 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 (daytime plus nighttime urine volume) in the elderly.[8] Disturbance of the circadian regulation of urine production may induce NP. Circadian regulation of plasma vasopressin is absent in elderly men and is the main causative factor of NP; therefore, most attention has focused on the use of desmopressin acetate for patients with NP.[9]

In patients with BPH, the use of α_1-AR antagonists has resulted in a modest improvement in nocturia,[10–12] although the mechanism of action of these antagonists remains unknown. In addition, to our knowledge, there are no reports on the long-term evaluation of nocturia in patients treated with α_1-AR antagonists using a frequency–volume chart (FVC).

A clear day/night pattern of catecholamine release and blood pressure exists in humans.[13,14] Although arginine vasopressin is the key hormone controlling the circadian rhythm of urine production, catecholamines seem to be associated with the circadian regulation of urine production. We therefore speculated that α_1-AR antagonists might improve nocturia by reducing nighttime urine production and

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increasing daytime urine production in BPH patients. In the present study, the long-term effect of tamsulosin treatment on nighttime urine production was assessed by measuring changes in FVC data over time. In addition, the mechanisms underlying the improvement of nocturia in BPH patients, especially those with NP, are discussed.

PATIENTS AND METHODS

In this prospective, open-label, single-arm study, participants received detailed information about the study procedure, and informed consent was obtained from all patients before the study. The study was approved by the ethics committee of our institution.

A total of 104 patients with LUTS secondary to untreated BPH diagnosed in the BPH outpatient clinic of Nagoya City University Hospital from 2002 to 2008 were enrolled. The BPH outpatient clinic is staffed by only one doctor (Y.K.). 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) <15 ml/sec, and prostate volume (PV) >20 ml. Patients with neuropathic disorders including diabetes mellitus or urinary tract infections were excluded. Six patients had received antihypertensive drugs. None of the patients had received α-AR antagonists, hormonal drugs acting on the autonomic nervous system, diuretics, or antidepressants.

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, and 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 screen for study eligibility, as described above. After enrollment in the study, the patients were treated with tamsulosin (Harnal; Astellas Pharma Inc., Tokyo, Japan) 0.2 mg once daily after breakfast. Standard doses of this drug as commonly used in clinical practice in Japan were chosen. Patient compliance was assured by pill counts. Improvements in IPSS, individual IPSS nocturia score, and QOL index were defined as the statistically significant decrease of these scores after tamsulosin treatment. Improvement in MFR was defined as the statistically significant increase of MFR after tamsulosin treatment.

Visits 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 FVC, and underwent uroflowmetry at enrollment and during every visit after pharmacologic treatment with tamsulosin. All patients were clinically assessed, with symptom severity measured using the IPSS. Patients recorded their voiding behavior on three 24-hr FVCs on consecutive days. For each day of the study, patients entered their waking time and bedtime, and volume of urine voided to the closest hour (measured using a calibrated jug). Patients were trained by a doctor (Y.K.) in completing the chart and were instructed to complete the FVCs within 4 days before their assessment at the outpatient department. There were no restrictions on type and timing of food and fluids. If the patients forgot to complete the 3-day FVC or failed to undergo uroflowmetry on visit day, they were asked to visit the outpatient clinic again within 7 days. Only patients receiving tamsulosin for over 24 months were evaluated in this study. During the study, prescription of other types of drugs was prohibited. The primary endpoint was the significant change in nighttime urinary volume 24 months after tamsulosin administration. Secondary endpoints were significant changes in IPSS, QOL, MFR, and FVC data including daytime/nighttime urine frequency, daytime and 24-hr urine volume, and maximum and mean voided volume 24 months after treatment. Analyses of the same parameters were also performed up to 48 months after treatment for patients who hoped to continue tamsulosin monotherapy beyond the 24-month study period.

The PSA value was checked every year. In cases in which the PSA value was >4 ng/ml during treatment, the patients were eligible to undergo prostate biopsy after digital rectal examination and ultrasonography. If prostate cancer was found, the patients were excluded from the study.

Data are expressed as the mean ± SD or median (interquartile range). To determine differences in the IPSS and QOL index between groups, the Mann–Whitney *U* test was used. To assess differences in voided volume, MFR and PVR and the parameters of FVC before and after treatment and between two groups, the paired *t*-test was used. A *P*-value of <0.05 was considered significant.

RESULTS

One hundred fifteen patients were assessed for eligibility and 11 patients were excluded before the study based on deviation from inclusion criteria (6) and withdrawal of consent (5). Although 104 patients were enrolled in this study, 22 (21%) patients failed to complete the 24 months of the study. Of these patients, 5 (5%) were found to have prostate cancer during the study, and 17 (16%) were discontinued before 24 weeks of tamsulosin treatment because of complete improvement of symptoms (3), insufficient therapeutic response (2), adverse events (1), failure to return to follow-up (2), death during the study period (2), and reasons not specified (7). Only one patient reported adverse events, dizziness, and orthostatic hypotension. Finally, 82 patients (mean age: 70.9 ± 7.1 years, mean prostate volume: 35.6 ± 16.0 ml) completed the 24 months of treatment (Table I). Because 53 patients hoped to receive tamsulosin monotherapy after the 24-month study period, the same analyses were conducted in these patients for an additional period, and the data obtained are shown in the figures.

Statistically significant improvement from the baseline was observed in total IPSS, QOL index, and MFR starting from 1 month after treatment, and these improvements were maintained for 48 months ($P < 0.05$). IPSS nocturia score statistically significantly improved for 48 months. No significant change in PVR was found in response to tamsulosin treatment for 48 months (Fig. 1).

On FVC analyses, mean nighttime urine frequency decreased in patients treated with tamsulosin for a period of 48 months ($P < 0.05$; Fig. 2), but no significant changes in daytime urine frequency were observed. Mean nighttime urine volume was also decreased after treatment for 48 months ($P < 0.05$). Maximum voided volume increased most months after treatment ($P < 0.05$). Mean nighttime voided volume also increased most months up to 24 months after treatment, but it was not detected until after 24 months.

On the basis of the baseline FVC data, the patients who completed the 24 months of treatment were divided into two groups, NP (n = 58) and nonNP (n = 24). NP was defined as a nocturnal urine fraction exceeding 33% of the daily output. We compared the change in IPSS, QOL, MFR, and FVC data between NP and nonNP groups 24 months after tamsulosin administration. As described above, analyses of the same

TABLE I. Baseline Characteristics of IPSS, QOL Index and Parameters of Uroflowmetry and Frequent-Volume Chart in Patients With and Without Nocturnal Polyuria

	All	Nocturnal polyuria	Nonnocturinal polyuria	*P*-value
Mean ± SD				
Number of Pts	82	58	24	
Age (years)	70.9 ± 7.1	71.9 ± 7.1	68.6 ± 6.8	0.0566[a]
Prostate volume (ml)	35.6 ± 16.0	35.7 ± 17.6	35.3 ± 11.6	0.9275[a]
IPSS (median (interquartile range))				
Incomplete emptying	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.5 (1.0,4.0)	0.1139[b]
Frequency	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.7717[b]
Intermittency	2.0 (1.0, 3.8)	2.0 (1.0, 3.0)	4.0 (2.0, 5.0)	0.2249[b]
Urgency	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	1.5 (0.8, 3.3)	0.9254[b]
Weak stream	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	4.0 (3.0, 5.0)	0.1717[b]
Straining	2.0 (1.0, 3.0)	1.5 (1.0, 2.0)	2.0 (1.0, 3.3)	0.1727[b]
Nocturia	3.0 (2.0, 3.8)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)	0.3995[b]
Total score	16.0 (13.0, 20.0)	16.0 (13.0, 18.8)	17.5 (15.8, 21.5)	0.0318[b]
QOL index	4.5 (4.0, 5.0)	4.5 (4.0, 5.0)	5.0 (4.0, 5.0)	0.2484[b]
Uroflowmetry (mean ± SD)				
MFR (ml/s)	7.8 ± 2.8	8.0 ± 3.0	7.2 ± 2.3	0.2125[a]
Voiding volume (ml)	152.5 ± 100.2	144.6 ± 90.1	171.7 ± 121.3	0.2676[a]
Post-void residual	32.8 ± 42.4	29.3 ± 40.1	41.4 ± 47.3	0.2404[a]
Frequency volume chart				
Day-time urine frequency (times)	8.1 ± 2.1	7.8 ± 1.8	9.0 ± 2.5	0.0181[a]
Night-time urine frequency (times)	2.0 ± 1.1	2.1 ± 1.1	1.8 ± 1.0	0.1345[a]
24-hr frequency (times)	10.1 ± 4.7	9.9 ± 4.6	10.7 ± 5.8	0.1892[a]
Day-time urine volume (ml)	1070.5 ± 421.2	972.3 ± 341.7	1307.9 ± 502.2	0.0008[a]
Night-time urine volume (ml)	569.2 ± 232.9	614.5 ± 239.6	459.8 ± 176.2	0.0055[a]
24-hr urine volume (ml)	1639.8 ± 819.0	1586.8 ± 784.5	1767.7 ± 994.0	0.1581[a]
Day-time urine volume per void (ml)	135.5 ± 74.7	127.9 ± 69.4	153.9 ± 91.4	0.0564[a]
Night-time urine volume per void (ml)	201.3 ± 112.0	210.5 ± 118.8	179.1 ± 102.0	0.2683[a]
Maximum voided volume (ml)	242.8 ± 114.2	254.0 ± 113.0	215.8 ± 115.0	0.1705[a]

Nocturia polyuria versus nonnocturnal polyuria.
[a]*t*-Test.
[b]Wilcoxon rank sum test.

parameters were also performed up to 48 months after treatment for patients who hoped to continue tamsulosin monotherapy beyond the 24-month study period in both groups.

Although IPSS was lower in the NP group than the nonNP group ($P < 0.05$), there was no significant difference in patient characteristics and other parameters, including IPSS individual scores, QOL index, and MFR before treatment (Table I). Daytime frequency and urine volume in the NP group was smaller than in the nonNP group ($P < 0.05$, $P < 0.001$, respectively). On the other hand, nocturnal urine frequency was comparable between the groups, although nocturnal urine volume in the NP group was statistically significantly larger ($P < 0.01$). No significant difference was found in 24-hr urine volume and maximum voided volume between groups.

The IPSS, QOL index, and MFR showed statistically significant improvements most months after treatment in both groups (Fig. 1). The IPSS nocturia score also showed a statistically significant improvement approximately 3 years after treatment in both groups.

The change in each parameter of the FVC after tamsulosin treatment in NP and nonNP patients is shown in Figure 2. Mean daytime urine frequency did not change 24 months after treatment in the NP group, but showed a statistically significant decrease 24 months after treatment in the nonNP group. A change in daytime urine frequency from the baseline in the nonNP group was statistically significantly larger than in the NP group 24 months after treatment. Mean nighttime urine frequency on FVC showed a statistically significant decrease 24 and 48 months after treatment in both the NP and nonNP groups. Changes in nighttime urine frequency were not significantly different between groups. Mean daytime urine volume showed a statistically significant increase in the NP group 24 and 48 months after treatment, while this was not found in the nonNP group. A change in daytime urine volume from the baseline in the NP group was statistically significantly larger than in the nonNP group 24 months after treatment. A statistically significant decrease in nighttime urine volume was detected in the NP group after 48 months of treatment, although this decrease was not found in the nonNP group. The change in nighttime urine volume in the NP group from the baseline was statistically significantly larger than in the nonNP group most months after treatment. None of the groups showed statistically significant changes in the 24-hr urine volume after treatment. Maximum voided volume was significantly increased most months after treatment in both groups. A change in maximum voided volume from the baseline in the nonNP group was statistically significantly larger than in the NP group 24 months after treatment. Mean nighttime voided volume was increased after both 24 and 48 months of treatment in the nonNP groups, suggesting that increased mean nighttime voided volume may be one of the factors contributing to decreased nocturia in the nonNP group.

DISCUSSION

In the present study, we demonstrated that tamsulosin improved LUTS and QOL as well as MFR for 48 months, which supported its long-term usefulness as first-line therapy for LUTS/BPH.

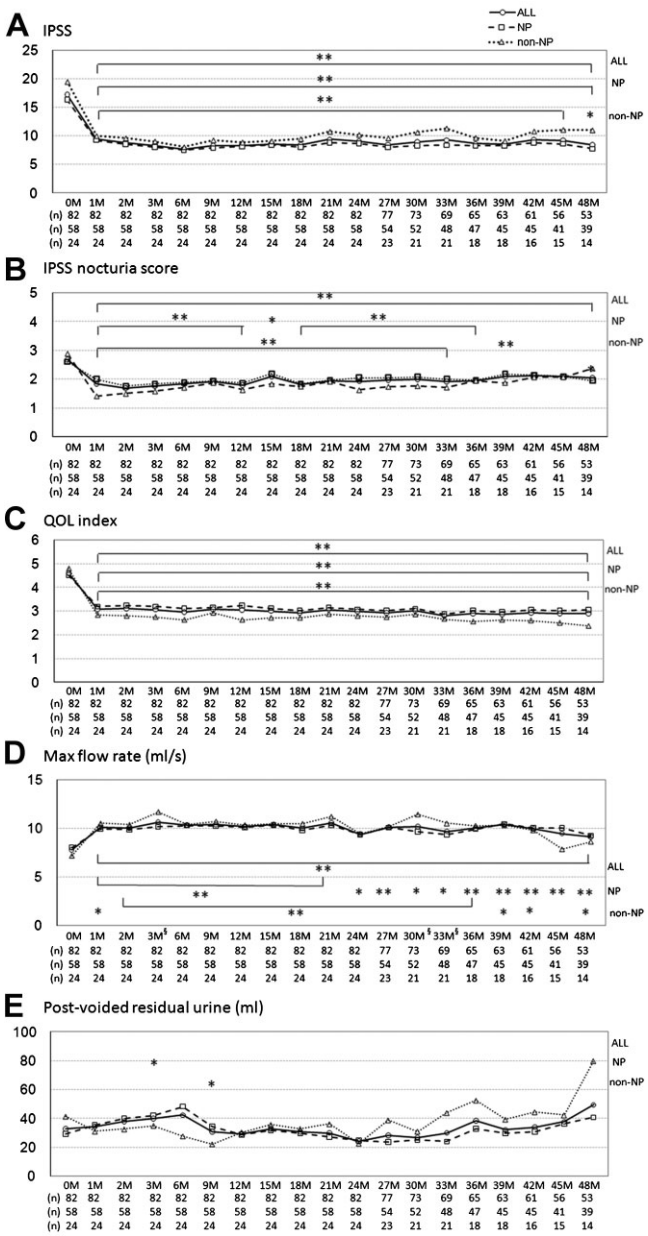

Fig. 1. Changes in IPSS, IPSS nocturia score, QOL index, MFR, and PVR after tamsulosin treatment in NP and nonNP patients. $^{*}P < 0.05$, $^{**}P < 0.01$ versus baseline. $^{\S}P < 0.05$, $^{\S\S}P < 0.01$, NP versus nonNP (mean change from baseline). **A**–**C**: Wilcoxon signed ranks test. **D**,**E**: paired *t*-test.

Nocturia is a common manifestation of BPH, which is not only irritating for patients but can also have a marked impact on their QOL and sleep patterns.[15] Because BPH is a potential risk factor for nocturia, α_1-AR antagonists are considered a potential treatment for nocturia.[10–12,16] However, the relief of bladder outlet obstruction is not sufficient to correct nocturia. Yoshimura et al.[16] reported that tamsulosin treatment reduced the number of episodes of nocturia in 17.9% of patients, but the improvement rates were lowest for nocturia among the seven individual scores of IPSS. Homma et al.[17] reported that the IPSS nocturia score was different from other symptom scores, as nocturia was the least specific symptom associated with BPH and was least sensitive to conventional BPH treatment. Because the pathogenesis of nocturia in BPH patients is multifactorial, a careful evaluation of each patient aimed at finding the etiology of nocturia is important to determine the appropriate treatment in each case. In the present study, although the nocturia score on the IPSS was also significantly reduced by long-term tamsulosin treatment, our main concern was to evaluate the mechanisms underlying the improvement in nocturnal polyuria by long-term tamsulosin treatment.

A valuable tool for assessing and objectively evaluating nocturia is the FVC, which has been used to investigate possible causes of nocturia, including overall polyuria, NP, and reduced nocturnal bladder capacity.[18] We therefore analyzed the long-term outcome of tamsulosin treatment using the FVC. The present results showed that mean nighttime frequency and nighttime urine volume decreased, and maximum voided volume was increased during a treatment period of 48 months, suggesting that tamsulosin decreases nighttime frequency by decreasing nighttime volume and increasing bladder capacity.

Recently, NP has become a major concern in the diagnosis and treatment of nocturia. Disturbance of the circadian regulation of urine production may be one of the main factors contributing to NP. Abnormal secretion of arginine vasopressin, lifestyle, and dietary factors, congestive heart failure, low albumin, venous stasis disease, and high intake of salt, autonomic dysfunction, respiratory conditions such as sleep apnea, or kidney disorders are possible causes of NP.[5,6] At present, the main pharmacotherapeutic option for NP is desmopressin acetate. However, several reports on the efficacy of α_1-AR antagonists in the treatment of BPH patients with NP have recently been published. Takahashi et al.[19] reported that treatment with the α_1-AR antagonist naftopidil for 6 weeks decreased nocturnal urine volume in BPH patients with NP, although no statistically significant difference was found, and it was concluded that α_1-AR antagonists somehow affect urine output at night. Yoshida et al.[20] recently reported the effectiveness of 8-week tamsulosin treatment for patients with nocturia associated with LUTS/BPH, and demonstrated that tamsulosin improved nighttime frequency by decreasing nighttime urine volume. We therefore speculated that the effect of α_1-AR antagonists on nocturia could be related to the reduction of nighttime urine volume, and its efficacy might differ depending on patient characteristics, especially the presence or absence of NP. In the present study, patients were divided into two groups, NP and nonNP, and differences in the effectiveness of long-term tamsulosin administration between the groups were assessed. The IPSS, QOL index, and MFR improved for 48 months after treatment in both groups. Interestingly, however, in addition to a significant decrease in nighttime urine volume, a significant increase in daytime urine volume was detected in the NP group during a 48-month treatment period, and these changes were not found in the nonNP group. These data suggested that tamsulosin might act by correcting disturbances of the circadian regulation of urine production in BPH patients with NP for long periods after treatment.

The underlying pathophysiological condition in NP is the absence of circadian variation in urine production in elderly men.[21] Arginine vasopressin is the key hormone controlling the circadian rhythm of urine production; therefore, desmopressin acetate is currently the treatment of choice for NP. However, other factors, including catecholamine levels, are associated with the circadian rhythm of urine production. A positive correlation between nocturnal urine volume and daytime mean arterial blood pressure was reported.[22]

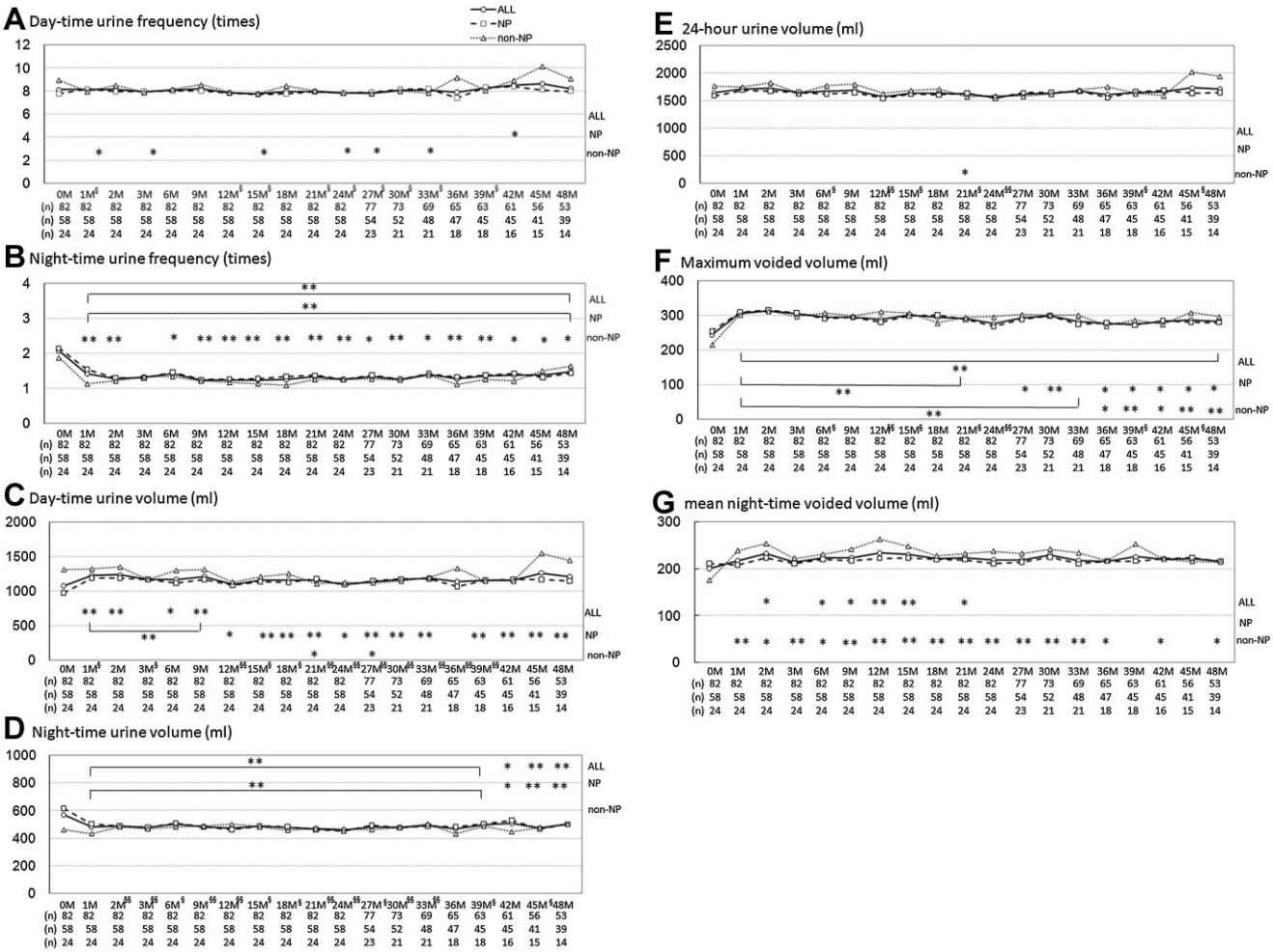

Fig. 2. Changes in the parameters of FVC after tamsulosin treatment in NP and nonNP patients. $^{*}P < 0.05$, $^{**}P < 0.01$ versus baseline. $^{\S}P < 0.05$, $^{\S\S}P < 0.01$, NP versus nonNP (mean change from baseline). Paired *t*-test.

Daytime arterial blood pressure was increased in patients with NP compared to controls.[22] Sugaya et al.[23] reported that daytime plasma noradrenaline levels and the edema ratio (the ratio of extracellular water to total body water) before sleeping were increased in elderly subjects with nocturia, although there was no significant difference in daytime urine production between elderly subjects with and without nocturia. These authors suggested that a decrease in the catecholamine level at night in elderly subjects could cause a decrease in renal arterial resistance, which would increase renal blood flow, resulting in an increase in urine production to excrete water stored during the night. This mechanism was suggested as one of the main factors contributing to an increased frequency of nocturnal urination in the elderly.[23] Some investigators reported that α_1-AR subtypes mediate smooth muscle contraction in the rat renal artery.[24–26] In our study, we demonstrated that tamsulosin reduced nighttime urine production in correlation with an increase in daytime urine production in BPH patients with NP. These results suggest that tamsulosin may act by increasing daytime renal blood flow by relaxing the renal artery, and decreasing the daytime extracellular water volume by increasing daytime urine production, which would decrease nighttime urine production and nocturia. However, definitive evidence has not been found. Because many factors are involved in the circadian regulation of urine output, further study will be needed.

CONCLUSIONS

In the present study, the long-term effectiveness of tamsulosin treatment in BPH patients was demonstrated. FVC is a useful tool for the evaluation of patient characteristics to enable the determination of efficient, individualized therapy regimens tailored to the needs of each BPH patient. Our long-term prospective study using FVC demonstrated that tamsulosin could correct disturbances of the circadian regulation of urine production in BPH patients with NP. However, other medical options may be needed to improve nocturia in BPH patients without NP based on the involvement of additional factors associated with bladder dysfunction, nighttime urine production, or sleep disturbances, which may contribute to nocturia.

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