Urologia Internationalis

Original Paper

Urol Int 2020;104:587–593
DOI: 10.1159/000506489

Received: December 19, 2019
Accepted after revision: April 2, 2020
Published online: June 2, 2020

Tadalafil Improves Nocturia and Nocturia-Related Quality of Life in Patients with Benign Prostatic Hyperplasia (KYU-PRO Study)

Ryosuke Takahashi[a] Yasuhiro Sumino[b] Minoru Miyazato[c] Hisae Nishii[d] Takuma Oshiro[f] Hiromitsu Mimata[e] Seiichi Saito[f] Masaki Yoshida[d] Masatoshi Eto[g]

[a]Department of Urology, Spinal Injuries Center, Iizuka, Japan; [b]Department of Urology, National Hospital Organization Oita Medical Center, Oita, Japan; [c]Department of Systems Physiology, Graduate School of Medicine, University of the Ryukyus, Nishihara, Japan; [d]Department of Urology, National Center for Geriatrics and Gerontology, Obu, Japan; [e]Department of Urology, Oita University Faculty of Medicine, Oita, Japan; [f]Department of Urology, Graduate School of Medicine, University of the Ryukyus, Nishihara, Japan; [g]Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Keywords
Nocturia · Quality of life · Hours of undisturbed sleep · Benign prostatic hyperplasia · Phosphodiesterase 5 inhibitor

Abstract
Introduction: Tadalafil improves lower urinary tract symptoms (LUTS) including nocturia. However, the effect of tadalafil on the nocturia-related quality of life (QoL) is still unknown. ***Objective:*** The effects of tadalafil on nocturia and nocturia-related QoL were evaluated prospectively in patients with benign prostatic hyperplasia (BPH) as a multicenter study. ***Methods:*** Eligible men were ≥40 years with nocturia ≥2 and a prostate volume ≥20 mL. Patients were asked to complete a self-report questionnaire on the International Prostate Symptom Score (IPSS), the Nocturia Quality of Life questionnaire (N-QoL) and the International Index of Erectile Function 5 (IIEF5). Urinary frequency volume charts (FVCs) were also evaluated. These measures were evaluated at baseline, and after 4, 8, and 12 weeks of tadalafil administration (5 mg once daily). ***Results:*** Thirty-one patients with a mean age of 74 years, a mean prostate volume of 31 mL, and a mean prostate-specific antigen level of 2.8 ng/mL were included. Treatment with tadalafil significantly improved their nocturia after 4 weeks, and these improvements were maintained for the 12-week treatment period. Total N-QoL score in new patients and several N-QoL items (inadequate sleep at night and overall bother) in all patients improved significantly after tadalafil treatment. FVCs revealed a significant improvement in the number of hours of undisturbed sleep (HUS) after treatment with tadalafil. No serious adverse events were observed. ***Conclusions:*** This study indicates that tadalafil 5 mg once daily improves nocturia, nocturia-related QoL, and HUS in BPH patients with nocturia. These results suggest that tadalafil can offer a clinically meaningful treatment option for BPH patients with nocturia.

Introduction

Night-time voiding (nocturia) is one of the most bothersome symptoms in men with lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH), and it

karger@karger.com
www.karger.com/uin

Ryosuke Takahashi, MD, PhD
Department of Urology, Spinal Injuries Center
550-4 Igisu, Iizuka, Fukuoka 820-8508 (Japan)
r-taka@uro.med.kyushu-u.ac.jp

is highly prevalent in community-dwelling men [1]. Pharmacological therapies with α1-blockers, antimuscarinics, or β3 agonists are often applied. However, the efficacy of these medications has not been sufficient [2], and alternative treatment options with a different action profile are needed.

Tadalafil, a long-acting phosphodiesterase type 5 (PDE5) inhibitor, has recently been approved worldwide for the treatment of LUTS/BPH. The main mechanism of action of tadalafil is enhancement of the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) signaling pathway [3], in contrast to other approved medications for LUTS/BPH. Other mechanisms including increased pelvic blood perfusion, modulation of the afferent nerves, and an anti-inflammatory effect have also been reported [3, 4]. We previously reported that tadalafil improves LUTS including nocturia, general health, and quality of life (QoL) after examining the subjective self-report questionnaires of patients with BPH/LUTS [5, 6]. Other papers have also reported the effect of tadalafil on nocturia in LUTS/BPH patients [7, 8]. However, Oelke et al. [7] stated that the treatment difference in nocturia is small and that the clinical significance of the improvements is questionable; this finding was likely influenced by the study designs, most of which did not test specifically for nocturia [7]. In addition, there have been no reports of the assessment of urinary frequency volume charts (FVCs) to evaluate tadalafil treatment for nocturia.

In this study, we included patients with nocturia ≥2, to examine the effects of tadalafil on nocturia in BPH patients using FVCs. We also evaluated QoL using the Nocturia Quality of Life questionnaire (N-QoL), a research tool for assessing the impact of nocturia on QoL.

Materials and Methods

Study Design

This open, multicenter, 12-week, prospective clinical study to examine the efficacy of tadalafil for treating nocturia was conducted at 4 institutes in Japan between November 2016 and December 2017.

Study Protocol

Eligible men were ≥40 years old with nocturia ≥2 and a prostate volume ≥20 mL. Those patients previously prescribed α1-blockers were changed to tadalafil after a washout period of 1 week. No patients were taking anticholinergics or β-3 agonists, but 1 was taking dutasteride (which was not discontinued during the study).

Tadalafil was administered at a dose of 5 mg once daily over 12 weeks. Nocturia was assessed as the overall night-time voiding frequency based on the International Prostate Symptom Score (IPSS) Q7. Efficacy measures included the IPSS, IPSS-QoL score, International Index of Erectile Function 5 (IIEF5), and N-QoL score, assessed at baseline and after 4, 8, and 12 weeks of therapy. The questionnaires were translated into Japanese, validated, and the reliability was confirmed [9–12]. FVCs (at least a 2-day bladder diary) and uroflowmetry were evaluated at baseline and at week 12. Exclusion criteria were contraindications to the study drugs, prostate carcinoma, and other urological diseases. Safety was evaluated based on subject-reported adverse events (AEs).

Table 1. Patient demographics and background

	All patients		New patients
	SAS (n = 31)	FAS (n = 29)	FAS (n = 19)
Demographics			
Age, years	73.8±6.4	74.0±6.5	74.1±6.8
BMI	23.5±3.0	23.5±3.0	23.3±2.3
Comorbidity			
Hypertension	11 (35)	10 (34)	7 (37)
Diabetes mellitus	5 (16)	5 (17)	4 (21)
Dyslipidemia	9 (29)	9 (31)	5 (26)
IPSS total score		16.9±6.5	15.8±5.0
IPSS-QOL score		4.9±1.0	5.0±0.9
IIEF5 score		8.1±6.0	7.8±6.4
Q_{max}, mL/s		12.1±6.5	15.7±5.2
PVR, mL		58.5±52.2	63.4±58.2
Prostate volume, mL		30.8±11.0	32.4±10.9
PSA, ng/mL		2.8±2.3	2.9±2.3

Values express mean ± SD or n (%). SAS, safety analysis set; FAS, full analysis set; PVR, postvoid residual urine volume; PSA, prostate-specific antigen.

Statistical Analysis

Efficacy was assessed on the full analysis set (FAS), defined as those patients who received tadalafil at least once and who had a baseline assessment and at least 1 other assessment. Assessments of safety and tolerability were based on all patients (safety analysis set; SAS). Data are expressed as mean ± standard deviation (SD). Changes of variables before and after tadalafil treatment were evaluated using the paired t test. All tests were two-sided, and p values <0.05 were considered to be statistically significant. All statistical analysis was carried out with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [13].

Results

Patient Characteristics

The characteristics of the 31 eligible patients are listed in Table 1. The majority of participants (n = 27; 87.1%) were older than 65 years. Two patients were excluded from the analysis of efficacy; 1 was lost to follow-up and

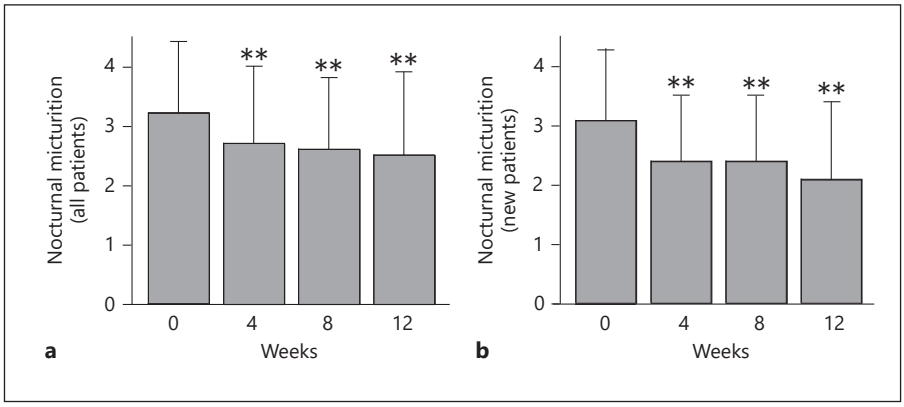

Fig. 1. Effect of tadalafil on nocturnal micturition in all patients (**a**) and new patients (**b**). Data are mean ± SD. ** $p < 0.01$, compared with baseline.

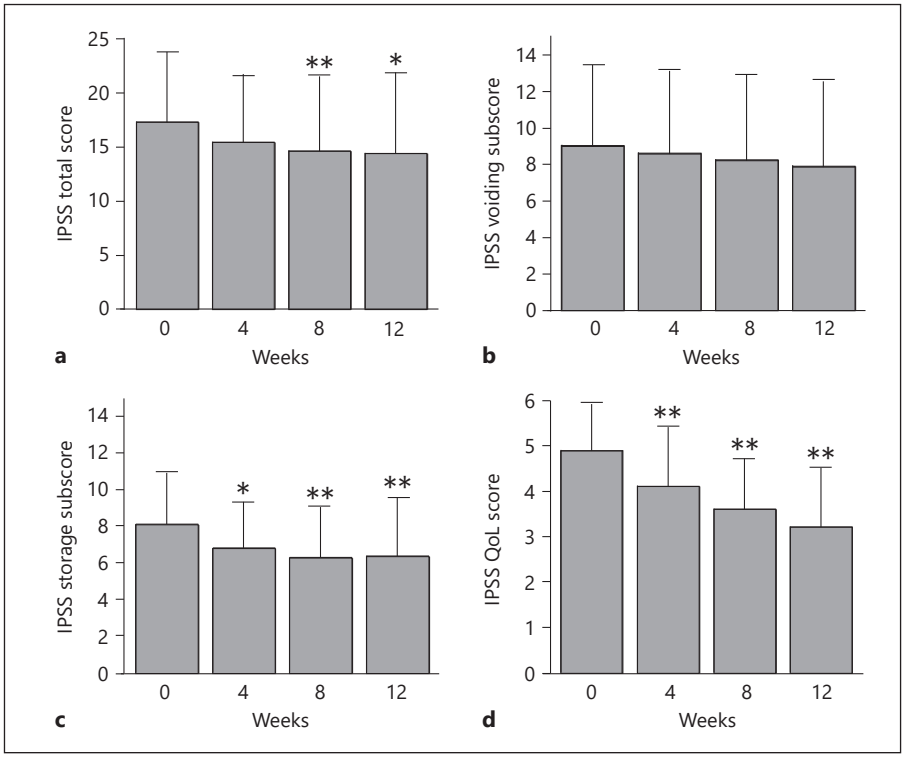

Fig. 2. Effect of tadalafil on IPSS total score (**a**), IPSS voiding subscore (**b**), IPSS storage subscore (**c**), and IPSS QoL score (**d**) in all patients. Data are mean ± SD. * $p < 0.05$, ** $p < 0.01$, compared with baseline.

1 discontinued treatment due to muscle pain before the first assessment at week 4. Altogether, 29 patients (94%) were subjected to the analysis of efficacy (all patients). Of these, 10 were changed to tadalafil from α1-blockers (6 on silodosin, 3 on tamsulosin, and 1 on naftopidil), and 19 had not had any previous treatment (new patients) and were analyzed separately.

Effect of Tadalafil on Nocturnal Micturition

A significant reduction in nocturnal micturition was observed at week 4 and continued throughout the treatment period, both overall and in the new patients (Fig. 1). Overall, the number of nocturnal micturitions decreased significantly from 3.1 ± 1.2 at baseline to 2.7 ± 1.3 ($p < 0.01$), 2.6 ± 1.2 ($p < 0.01$), and 2.5 ± 1.4 ($p < 0.01$) at 4, 8, and 12 weeks after treatment, respectively. In new patients, the number of nocturnal micturitions before tadalafil treatment was 3.1 ± 1.1, and this decreased significantly to 2.4 ± 1.1 ($p < 0.01$), 2.4 ± 1.1 ($p < 0.01$), and 2.1 ± 1.3 ($p < 0.01$) at 4, 8, and 12 weeks after treatment, respectively.

Effect of Tadalafil on LUTS in Patients with Nocturia

Overall, the IPSS storage subscore and IPSS-QoL score were significantly improved at week 4 and con-

Table 2. Effect of tadalafil on N-QoL in all patients

		Before	Week 4	Week 8	Week 12
Total score of N-QoL		69.2±15.7	71.0±20.9	68.4±19.5	72.5±18.5
Sleep/energy		76.9±13.7	74.2±20.4	74.5±19.6	79.5±16.4
Q1	Concentration	0.6±0.7	0.9±0.9	0.9±0.9	0.9±0.7
Q2	Low energy	0.8±0.8	0.9±1.0	1.0±0.8	0.9±0.8
Q3	Sleep during the day	1.3±1.0	1.2±1.2	1.1±1.0	1.1±0.9
Q4	Productiveness	0.5±0.7	0.9±0.9	0.8±0.9	0.5±0.6
Q5	Physical activities	0.5±0.7	0.8±1.1	1.1±1.1	0.6±0.9
Q7	Inadequate sleep at night	2.1±1.1	1.7±1.2	1.4±1.0*	0.9±1.0**
Bother/concern		61.5±21.4	67.9±23.8	62.2±21.8	65.5±21.7
Q6	Fluid restriction	0.9±0.9	0.9±1.0	1.1±0.9	0.9±0.9
Q8	Disturbance of others	1.5±2.0	1.4±2.0	1.6±2.2	1.4±2.4
Q9	Preoccupation with waking at night	0.9±1.0	0.8±0.9	0.9±0.9	0.9±1.1
Q10	Worry over condition worsening	1.9±1.1	1.5±1.2	1.9±1.0	1.6±1.1
Q11	Worried over treatment options	1.9±1.1	1.5±1.2	1.8±1.1	1.6±1.0
Q12	Overall bother	2.3±1.1	1.7±1.0*	1.9±0.9	1.9±0.9*
Q13	Overall impact on everyday life	3.8±2.1	3.9±2.6	3.8±2.6	3.3±2.4

Data are mean ± SD. * $p < 0.05$, ** $p < 0.01$, as compared with baseline.

tinued to improve throughout the treatment period (Fig. 2c, d). However, the IPSS voiding subscore gradually decreased but did not change significantly throughout the treatment period (Fig. 2b). In new patients, the effects of tadalafil on the IPSS total scores and subscores were almost the same as the effect overall (data not shown).

Q_{max} (at baseline: 12.1 ± 6.5 mL/s; at week 12: 12.3 ± 7.3 mL/ms) and postvoid residual urine volume (PVR) (at baseline: 58.5 ± 52.2 mL; at week 12: 37.8 ± 24.4 mL) improved numerically but did not change significantly with tadalafil treatment (data not shown). The IIEF5 total score (at baseline: 8.1 ± 6.0 mL/s; at week 12: 8.2 ± 7.4 mL/ms) did not change throughout the treatment (data not shown).

Effect of Tadalafil on Nocturia-Related QoL

Overall, the N-QoL total score and 2 domain scores (sleep/energy and bother/concern) did not improve significantly during the 12-week treatment with tadalafil. However, the N-QoL Q7 score (inadequate sleep at night) improved significantly at 8 ($p < 0.05$) and 12 ($p < 0.01$) weeks. In addition, the N-QoL Q12 score (overall bother) improved significantly at 4 ($p < 0.05$) and 12 ($p < 0.05$) weeks after the treatment with tadalafil (Table 2).

In new patients, the N-QoL total score improved significantly at week 12 ($p < 0.05$). The N-QoL Q7 score (inadequate sleep at night) improved significantly at 4 ($p < 0.01$), 8 ($p < 0.01$), and 12 ($p < 0.01$) weeks, and the N-QoL Q12 score (overall bother) improved significantly at 8 ($p < 0.05$) and 12 ($p < 0.05$) weeks. In addition, the N-QoL Q3 score (sleep during the day) at week 8 ($p < 0.05$) and the N-QoL Q13 score (overall impact on everyday life) at week 12 ($p < 0.05$) also improved significantly after the treatment with tadalafil (Table 3).

Effect of Tadalafil on FVC Parameters

FVCs were obtained from 26 patients. Hours of undisturbed sleep (HUS) improved significantly after treatment with tadalafil, both overall and in new patients (Table 4). Urine volume voided/voiding at night improved numerically, but no significant difference was observed. Other factors, including the daytime, nocturnal, and 24-h urine volumes and the nocturnal polyuria index (NPi, i.e., nocturnal urine volume/24-h urine output) did not change significantly after the treatment with tadalafil (Table 4).

Safety and Tolerability

Headache was the most common AE ($n = 2$). Dizziness ($n = 1$), dyspepsia ($n = 1$), itching ($n = 1$), muscle pain ($n = 1$), and general fatigue ($n = 1$) were also observed. Discontinuation due to AEs occurred in 7 patients (2 cases of headache and 1 case each of dizziness, dyspepsia, itching, muscle pain, and general fatigue). However, there were no clinically severe AEs.

Table 3. Effect of tadalafil on N-QoL in new patients

		Before	Week 4	Week 8	Week 12
Total score of N-QoL		65.6±15.0	69.8±22.4	70.4±22.4	74.0±19.1*
Sleep/energy		74.7±12.7	76.0±22.2	77.9±21.8	82.1±15.8
Q1	Concentration	0.7±0.7	0.9±1.0	0.8±1.0	0.8±0.7
Q2	Low energy	0.9±0.8	0.8±1.0	1.0±0.9	0.9±0.8
Q3	Sleep during the day	1.4±1.0	1.2±1.3	0.9±1.0*	1.0±0.9
Q4	Productiveness	0.4±0.6	0.8±0.9	0.7±1.0	0.4±0.5
Q5	Physical activities	0.3±0.5	0.5±1.0	0.7±1.1	0.4±0.7
Q7	Inadequate sleep at night	2.3±0.6	1.5±1.2**	1.2±0.9**	0.8±1.0**
Bother/concern		56.6±20.8	63.5±24.6	62.9±25.0	65.8±23.4
Q6	Fluid restriction	1.1±1.0	0.9±1.0	1.1±0.9	0.9±0.9
Q8	Disturbance of others	2.0±2.3	1.8±2.4	2.0±2.6	1.6±2.7
Q9	Preoccupation with waking at night	0.9±1.0	1.0±0.9	1.0±1.0	1.2±1.2
Q10	Worry over condition worsening	2.1±1.0	1.6±1.3	1.7±1.1	1.4±1.1
Q11	Worried over treatment options	1.9±1.0	1.7±1.2	1.6±1.2	1.4±1.0
Q12	Overall bother	2.4±1.0	1.8±1.0	1.7±1.0*	1.7±0.9*
Q13	Overall impact on everyday life	4.5±1.9	4.1±2.4	3.8±2.6	3.1±2.3*

Data are mean ± SD. * $p < 0.05$, ** $p < 0.01$, compared with baseline.

Table 4. Effect of tadalafil on FVC variables in all patients and new patients

	Before	Week 12	*p* value
All patients			
HUS, min	149±61	189±80**	0.005
Urine volume voided/voiding at night, mL	191±80	208±70	0.13
Daytime urine volume, mL	1,103±485	1,020±520	0.20
Nocturnal urine volume, mL	676±243	664±271	0.43
24-hr urine volume, mL	1,782±531	1,695±670	0.17
NPi, %	38±12	39±14	0.81
New patients			
HUS, min	165±64	216±80**	0.006
Urine volume voided/voiding at night, mL	189±91	220±78	0.17
Daytime urine volume, mL	1,117±531	1,120±580	0.71
Nocturnal urine volume, mL	608±208	629±278	0.70
24-hr urine volume, mL	1,735±619	1,764±767	0.67
NPi, %	35±10	35±13	0.35

Data are mean ± SD. ** $p < 0.01$, as compared with baseline. HUS, hours of undisturbed sleep; NPi, nocturnal polyuria index.

Discussion

This prospective, multicenter clinical study examined the efficacy of tadalafil 5 mg once daily on nocturia in BPH patients. Our results indicate that (1) nocturia improved significantly after 4 weeks of treatment with tadalafil and was maintained for the 12-week treatment period, (2) total N-QoL score in new patients and several N-QoL items (inadequate sleep at night and overall bother) overall improved significantly, and (3) HUS were prolonged significantly after the treatment.

Nocturia improved significantly from baseline to week 12 after treatment with tadalafil. This finding is consistent with previous studies on tadalafil 5 mg [7, 8]. The magnitude of improvement from baseline to the end point (IPSS Q7: –0.6) and the onset of improve-

ment (at week 4) were similar to those of other tadalafil studies [7, 8].

We attempted to evaluate the changes in nocturia-related QoL using the N-QoL questionnaire, which has been confirmed to be a useful tool for the evaluation of nocturia in Japanese patients [14]. The N-QoL Q7 score (inadequate sleep at night) and N-QoL Q12 score (overall bother) improved significantly after treatment with tadalafil (Tables 2, 3). This is possibly the first study showing the positive effects of tadalafil on nocturia-related QoL. No significant improvement was observed in the overall total N-QoL score (Table 2). However, in new patients, the total N-QoL score improved significantly at week 12 (Table 3). In addition, other items in the N-QoL scores (Q3: sleep during the day, Q13: overall impact on everyday life) improved significantly in new patients (Table 3). These results indicate that treatment with tadalafil improves not only nocturia but also the nocturia-related QoL, suggesting that tadalafil could be a clinically meaningful treatment for patients with nocturia. The findings also suggest that the improvement in QoL was better for new patients than for those who changed to tadalafil from another medication.

We also evaluated FVCs and explored the pathophysiology of the tadalafil-induced improvement on nocturia. As shown in Table 4, HUS, which are considered to be one of the key factors for nocturia-related QoL [15, 16], improved significantly both overall and in new patients, and this is one of the most important reasons for improvements in nocturia-related QoL with tadarafil treatment (Table 2, 3). We also anticipated that urine volume voided/voiding at night or nocturnal urine volume would change before and after treatment with tadalafil. Unfortunately, neither factor changed significantly after treatment with tadalafil (Table 4). However, as shown in Figure 2c, the IPSS storage subscore and urgency symptom (IPSS Q4: data not shown) improved significantly, and although the urine volume voided/voiding at night did not show a significant improvement, it did show a numerical improvement (Table 4). Based on these results, we speculate that the combined effects of these findings might explain the improvement of nocturia after treatment with tadalafil. In addition, although the major mechanism of action of tadalafil is the relaxation of the bladder outlet, other mechanisms including increased pelvic blood flow, modulation of the afferent nerves, and an anti-inflammatory effect have also been reported [3, 4]. This wide variety of mechanisms might be useful for the improvement of nocturia and nocturia-related QoL after treatment with tadalafil.

The IPSS voiding subscore (Fig. 2b) and IIEF score (data not shown) did not improve significantly after treatment with tadalafil, and this is not consistent with previous studies [5, 6, 17–20]. The precise reason for this discrepancy was not clear, but the patients included in our study were considerably older (mean age 74 years) and their IPSS voiding score (8.9 ± 4.4) and IIEF5 score (8.1 ± 6.0) before treatment were relatively lower than those in previous studies [17–20]. These factors might have affected our results.

The study had several limitations. First, this was a non-placebo study and the number of patients was small. Therefore, the possibility that the results could have been affected by some placebo effects cannot be excluded and a future study involving a larger number of patients is desirable. Second, nocturia was assessed from the overall night-time voiding frequency based on IPSS Q7, because FVCs were not obtained from all patients. Third, as the treatment period was 12 weeks, the long-term effects of tadalafil still need to be examined. Despite these limitations, we believe that the outcomes are of significance because this prospective study was the first to evaluate FVCs and nocturnal QoL using the N-QoL questionnaire after tadalafil treatment in BPH patients with nocturia.

In conclusion, this study indicated that tadalafil improves nocturia and nocturia-related QoL, suggesting that tadalafil can offer a clinically meaningful treatment option for patients with nocturia.

Acknowledgement

We would like to thank all patients and physicians for their contribution to this study. This work was supported by a Grant-in-Aid for Scientific Research (No. 18K10749).

Statement of Ethics

The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of Kyushu University Graduate School of Medical Sciences (IRB No. 28-287). All patients provided written informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have not had any funding for this study.

Author Contributions

All authors contributed equally to data collection and preparation of the manuscript.

References

1 Oelke M, Wiese B, Berges R. Nocturia and its impact on health-related quality of life and health care seeking behaviour in German community-dwelling men aged 50 years or older. World J Urol. 2014 Oct;32(5):1155–62.
2 Weiss JP, Blaivas JG, Bliwise DL, Dmochowski RR, Dubeau CE, Lowe FC, et al. The evaluation and treatment of nocturia: a consensus statement. BJU Int. 2011 Jul;108(1):6–21.
3 Giuliano F, Ückert S, Maggi M, Birder L, Kissel J, Viktrup L. The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. Eur Urol. 2013 Mar;63(3):506–16.
4 Vignozzi L, Gacci M, Cellai I, Morelli A, Maneschi E, Comeglio P, et al. PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. Prostate. 2013 Sep;73(13):1391–402.
5 Miyazato M, Oshiro T, Saito S, Takahashi R, Masatoshi E, Nishii H, et al. Effects of switching from alpha-blocker to tadalafil in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (kyu-pro study). Nishinihon J Urol. 2016;78:398–405.
6 Takahashi R, Miyazato M, Nishii H, Sumino Y, Takayama K, Onzuka M, et al. Tadalafil improves symptoms, erectile function and quality of life in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (KYU-PRO STUDY). Low Urin Tract Symptoms. 2018 Jan;10(1):76–83.
7 Oelke M, Weiss JP, Mamoulakis C, Cox D, Ruff D, Viktrup L. Effects of tadalafil on nighttime voiding (nocturia) in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a post hoc analysis of pooled data from four randomized, placebo-controlled clinical studies. World J Urol. 2014 Oct;32(5):1127–32.
8 Yoshida M, Origasa H, Seki N. Comparison of silodosin versus tadalafil in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia. Low Urin Tract Symptoms. 2017 Sep;9(3):176–86.
9 Homma Y, Tsukamoto T, Yasuda K, Ozono S, Yoshida M, Shinji M. Linguistic validation of Japanese version of International Prostate Symptom Score and BPH impact index. Nihon Hinyokika Gakkai Zasshi. 2002;93(6):669–80. Japanese.
10 Kimoto Y. International Index of Erectile Function (IIEF) and IIEF5. Nihon Rinsho. 2002 Jun;60 Suppl 6:112–6. Japanese.
11 Yoshida M, Gotoh M, Homma Y, Honda K, Nomiya M, Yamaguchi O, et al. Development and linguistic validation of the Japanese version of the nocturia quality of life questionnaire (N-QoL). Nihon Hainyokinou Gakkaishi. 2009;20(2):317–24. Japanese.
12 Ikeda T, Kobayashi M, Shimizu T, Yoshida M, Gotoh M, Homma Y, et al. Evaluation of psychometric properties of the Japanese version of the nocturia quality of life questionnaire (N-QoL). Nihon Hainyokinou Gakkaishi. 2009;20(2):325–31. Japanese.
13 Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013 Mar;48(3):452–8.
14 Yamanishi T, Fuse M, Yamaguchi C, Uchiyama T, Kamai T, Kurokawa S, et al. Nocturia Quality-of-Life questionnaire is a useful tool to predict nocturia and a risk of falling in Japanese outpatients: a cross-sectional survey. Int J Urol. 2014 Mar;21(3):289–93.
15 Chartier-Kastler E, Chapple CR. LUTS/BPH in clinical practice: the importance of nocturia and quality of sleep. Eur Urol Suppl. 2006;2:3–8.
16 Chartier-Kastler E, Tubaro A. The measurement of nocturia and its impact on quality of sleep and quality of life in LUTS/BPH. Eur Urol Suppl. 2006;5(1):3–11.
17 Yokoyama O, Yoshida M, Kim SC, Wang CJ, Imaoka T, Morisaki Y, et al. Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men. Int J Urol. 2013 Feb;20(2):193–201.
18 Takeda M, Yokoyama O, Lee SW, Murakami M, Morisaki Y, Viktrup L. Tadalafil 5 mg once-daily therapy for men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results from a randomized, double-blind, placebo-controlled trial carried out in Japan and Korea. Int J Urol. 2014 Jul;21(7):670–5.
19 Giuliano F, Oelke M, Jungwirth A, Hatzimouratidis K, Watts S, Cox D, et al. Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study. J Sex Med. 2013 Mar;10(3):857–65.
20 Porst H, McVary KT, Montorsi F, Sutherland P, Elion-Mboussa A, Wolka AM, et al. Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. Eur Urol. 2009 Oct;56(4):727–35.