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Original Article

The effect of α-blocker therapy on erectile functions in patients with lower urinary tract symptoms due to benign prostate hyperplasia

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Abstract

In this study we aimed to evaluate the impact of doxazosin treatment on erectile functions in patients with lower urinary tract symptoms (LUTS) and having erectile dysfunction (ED) at baseline. Fifty-three patients with LUTS (IPSS score > 7) whose maximum flow rate (Q_{max}) < 15 mL s^{-1} and PSA < 4 ng dL^{-1} were enrolled in the study. Patients received doxazosin 4 mg once daily for 6 weeks. Subjective efficacy was assessed by IPSS, IPSS-Quality of Life (IPSS-QoL) for LUTS and efficacy was assessed by International Index of Erectile Function (IIEF) for erectile functions at baseline and sixth weeks. The objective efficacy was assessed by Q_{max}. The patients were classified according to their self reported erectile status: group I had ED and group II did not have ED. At the endpoint, doxazosin significantly improved the total IPSS score (–7.7 ± 6.1, P = 0.006), IPSS-QoL score (–1.5 ± 1.5, P = 0.024) and Q_{max} (3.2 ± 4.6 mL s^{-1}, P = 0.002) over baseline. Mean decrease in IPSS and IPSS-QoL scores after the treatment period were 6.9 ± 6.4 (P < 0.001) and 0.95 ± 1.80 (P < 0.05) in group I, whereas 8.2 ± 5.8 (P < 0.001) and 1.9 ± 1.1 in group II (P < 0.001), respectively. Mean changes of Q_{max} values were 2.3 ± 3.3 mL s^{-1} in group I (P < 0.05) and 3.7 ± 5.3 mL s^{-1} in group II (P < 0.001). The improvement of IIEF-EF scores after the treatment period was only significant for group I. The efficacy of α-blocker therapy for LUTS was better by means of symptomatic relief for patients who did not have ED when compared with patients who had ED at baseline. However, slight improvement in erectile functions with α-blocker therapy was only seen in LUTS patients with ED.

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1 Introduction

Benign prostate hyperplasia (BPH) and erectile dysfunction (ED) are highly prevalent disorders in men and increase with age [1, 2]. BPH is characterized by reduced urinary flow rates and the presence of several Lower urinary tract symptoms (LUTS). Both the disorders have major impact on the quality of life (QoL). Worsening of QoL measures, including general health status, sexual satisfaction and sexual drive, correlate strongly with increasing severity of LUTS [3].

It is well recognized that various treatment strategies for the management of BPH may affect sexual functions [4]. BPH therapy aims to balance symptom relief and benefits on disease progression with side effects, QoL and sexuality. The clinical symptoms of BPH result from bladder outlet obstruction arising because of anatomical obstruction from the enlarged prostate and dynamic obstruction related to prostatic, smooth muscle

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tone variations mediated through α1-adrenoceptors of the sympathetic nervous system [5]. Selective α1-adrenoceptor antagonists (alfuzosin, doxazosin, tamsulosin and terazosin), the most common treatment options in patients with BPH, are important medical options in the management of BPH. These agents reduce smooth muscle tone in the prostate and lower urinary tract by inhibiting sympathetic α1-adrenoceptor stimulation, thereby relaxing the bladder outlet and improving urinary flow.

α1-Adrenoceptor antagonists also differ in their impact of sexual function. On the basis of the results of single-arm meta-analysis conducted by the 2003 American Urological Association (AUA) guideline panel, the median frequency of ED was similar during treatment with alfuzosin (3%), doxazosin (4%), tamsulosin (4%), terazosin (5%) and placebo (4%). The selective α1-adrenoceptor antagonist doxazosin mesylate is effective and well tolerated in the treatment of BPH, producing marked symptomatic relief and significant improvement in urinary flow rates [6]. On the basis of the results of combined analysis of two studies conducted by Kirby *et al.* [7], doxazosin improves sexual functions in BPH patients with sexual dysfunction at baseline. In this study, we aimed to compare the effects of doxazosin improving LUTS and erectile functions in BPH patients with and without ED at baseline.

2 Materials and methods

2.1 Eligibility criteria and treatment

Our study population consisted of 64 male patients aged > 40 years who had been in a steady sexual relationship for the past 6 months and were admitted to urology clinics with complaints of BPH (IPSS score > 7, maximum flow rates (Q_{max}) of ≥ 5 mL s^{-1} and ≤ 15 mL s^{-1} for a total voided volume of ≥ 150 mL and prostate-specific antigen (PSA) < 4 ng per 100 mL). The exclusion criteria were severe genital anatomic deformities that effect erectile function; a history of major pelvic surgery; patients taking medications, including 5-α reductase inhibitors, α-adrenoceptor blockers and phosphodiesterase type 5 (PDE5) inhibitors; patients with a diagnosis of congestive heart failure, bronchial asthma, coronary heart diseases, malignancy, liver cirrhosis, known malignant disease, including prostate cancer or chronic renal failure. Other criteria for exclusion were conditions that may cause LUTS and reduced urinary flow rates other than BPH such as large bladder diverticulum, urethral stricture, bladder stone, recurrent urinary tract infections, recurrent catheterization, active urinary tract infection and neurogenic bladder.

Doxazosin (Cardura, Pfizer, NY, USA) 4 mg once daily was prescribed to the patients. After a 6-week treatment course, patients were re-evaluated. Our retrospective study protocol was conducted in accordance with the declaration of Helsinki and local laws. After informing the patients about the study, their verbal consent was taken.

2.2 Evaluation procedure

The initial visit included a complete medical and sexual history and physical examination with digital rectal examination. Patients were assessed by International Prostate Symptom Score (IPSS) for LUTS. Standard laboratory testing, urinalysis, total and free PSA testing, urinary flow rate, post-voided residual urine, LUTS evaluation and prostate volume measurements by abdominal ultrasonography in accordance with the European Association of Urology (EAU) and AUA clinical guidelines for BPH were done.

Patients were grouped into two groups according to their self-reported erectile status. ED was identified by asking whether they have ED or not as 'Do you think you have ED?'. Group I indicated patients who reported the prescence of ED and group II indicated patients who reported the absence of ED. To measure the effect of doxazosin treatment on erectile functions, patients were also assessed using International Index of Erectile Function (IIEF) at baseline and at the end of treatment period. The erectile function (EF) domain consists of questions 1–5 and 15 aimed to assess EF. ED was diagnosed according to IIEF when total of IIEF-EF domain scores were < 26 points. The scoring of the IIEF-EF domain allowed classification of each patient as having no (26–30), mild (17–25), moderate (11–16) or severe (1–10) ED. Adverse events were assessed at the end of the treatment course.

2.3 Statistical analysis

Subjective efficacy was assessed by IPSS and IPSS-QoL scores and objective efficacy were assessed by Q_{max} at baseline and at 6 weeks for LUTS and efficacy was assessed by IIEF for erectile functions. The mean changes from baseline to the sixth week visit for the IPSS, QoL and Q_{max} in the population served as efficacy

outcomes.

Descriptive statistics were used to characterize variables in the population and in each group of treatment (mean ± SD). The characteristics and laboratory findings of the patients were assessed using the Mann–Whitney *U*-test. Mean changes adjusted for baseline are presented and tested using the Wilcoxon signed-rank test. All statistical tests were two-tailed with $P < 0.05$ as significance for treatment effects.

3 Results

A total of 64 consecutive patients who responded to the inclusion criteria were enrolled in the study and were randomized to treatment. Of these patients, 53 completed 6-week treatment course were included for data analysis. The most common causes of discontinuation from the study included lost to follow-up and protocol violations, and insufficient clinical response.

Mean ages were 64.8 ± 7.6 (range 51–77) years and 57.9 ± 6.4 (range 50–74) years in group I and II, respectively ($P = 0.001$). The prevalence of ED was detected to be 58.5% ($n = 31$), according to patient-reported erectile status, whereas the prevalence of ED was detected to be 71.7% ($n = 38$), according to IIEF-EF domain score (< 26). Mean IIEF-EF domain score was 10.8 ± 7.3 (range 1–27) in group I and 22.6 ± 7.2 (range 1–30) in group II. Of the respondents who reported the absence of ED, 32% had mild ED, and 14% had moderate to severe ED, as defined by the IIEF-EF criteria. Patients' demographics and baseline evaluation data for BPH were given in Table 1. There were no statistically significant differences between the compared parameters at baseline evaluation, excluding age and all IIEF domain scores.

BPH symptoms were considerably improved with doxazosin, as mean reductions in total IPSS and QoL were −7.7 ± 6.1 ($P = 0.006$) and 1.5 ± 1.5 ($P = 0.024$) over baseline, respectively. In addition, doxazosin

Table 1. Baseline characteristics of the groups according to self-reported erectile status.

	Group I	Group II	*P*-value*
n (%)	31 (58.5)	22 (41.5)	
Age (years)	64.8 ± 7.6	57.9 ± 6.4	0.001
BPH duration (months)	27.3 ± 24.3	23.6 ± 15.3	0.832
Smoking (packet per year)	0.23 ± 0.43	0.23 ± 4.3	0.990
Cardiovascular disease (%)	45.5	41.9	0.799
Diabetes mellitus (%)	13.6	9.7	0.654
PSA (ng mL^{-1})	2.0 ± 2.2	2.4 ± 2.5	0.321
Prostate volume (mL)	36.7 ± 14.8	37.8 ± 18.1	0.921
Q_{max} (mL s^{-1})	12.2 ± 2.5	11.7 ± 2.7	0.554
AFR (mL s^{-1})	5.6 ± 1.5	5.7 ± 1.8	0.707
VV (mL)	281.8 ± 113.2	316.9 ± 168.9	0.718
PVR (mL)	49.4 ± 57.0	61.5 ± 53.2	0.711
$IPSS_{total}$	16.2 ± 4.8	17.2 ± 6.1	0.883
QoL	3.6 ± 0.9	3.9 ± 1.1	0.309
IIEF-EF	10.8 ± 7.3	22.6 ± 7.2	< 0.001
IIEF-OF	4.2 ± 3.4	7.5 ± 2.5	0.001
IIEF-SD	5.6 ± 2.3	7.5 ± 1.5	0.002
IIEF-IS	4.7 ± 4.4	9.7 ± 3.2	< 0.001
IIEF-OS	5.0 ± 2.6	6.9 ± 2.3	0.011

Abbreviations: AFR, average flow rate; BPH, benign prostate hyperplasia; IPSS, International Prostate Symptom Score; IIEF-EF, International Index of Erectile Function-Erectile Function; IIEF-IS, International Index of Erectile Function-Intercourse Satisfaction; IIEF-OF, International Index of Erectile Function-Orgasmic Function; IIEF-OS, International Index of Erectile Function-Overall Satisfaction; IIEF-SD, International Index of Erectile Function-Sexual Desire; PSA, prostate-specific antigen; PVR, post-voided volume; Q_{max}, maximum flow rate; QoL, quality of life; VV, voided volume.

Data were expressed as mean ± SD.

*Mann–Whitney *U*-test.

produced significant improvements in Q_{max} of 3.2 ± 4.6 mL s^{-1} from baseline ($P = 0.002$).

Mean change in IPSS and QoL scores, Q_{max} and average flow rate after treatment was given in Table 2. The improvements from baseline to the end of doxazosin treatment were statistically significant for all parameters in both groups ($P < 0.01$). Although the improvements of LUTS due to doxazosin treatment were better in group II, the only significance between group I and II was detected for QoL ($P = 0.018$).

Mean IIEF-EF domain score increased in group I, whereas slightly decreased in group II after the doxazosin treatment from baseline (Table 2). Mean changes of other IIEF domains were not significant for both groups.

In all, mean change of IIEF-EF domain score from baseline, which was stratified according to ED severity using IIEF scores, was 4.3 ± 6.0, 0.3 ± 5.3 and −1.2 ± 1.6 in severe ($n = 14$), moderate ($n = 15$) and mild ($n = 9$) ED groups, respectively (Kruskall–Wallis; $P = 0.018$).

When IPSS was divided into obstructive and irritative sub-scores, mean IPSS voiding and IPSS storage sub-scores of group I and II were 10.8 ± 4.6, 6.4 ± 2.4 and 9.1 ± 3.1, 7.1 ± 3.0, respectively. The differences of the groups were not significant. In addition, the correlation analysis between baseline and mean changes of IIEF-EF domain scores, and between IPSS voiding and storage sub-scores were not significant, either.

No serious adverse events were observed during the treatment course in both groups.

4 Discussion

This study shows that ED diagnosed using IIEF-EF domain score is more prevalent than patients' reported of having ED in men with LUTS. In addition, the prevalence of self-reported ED in BPH patients is likely to underestimate the true prevalence of ED. The data presented here show that doxazosin 4 mg once daily administered for a short time is effective in improving LUTS and QoL, and is well tolerated. Doxazosin improved the erectile function that was evaluated by IIEF-EF domain score in those having concomitant ED.

In our study, we directly compared the efficacy and safety of doxazosin 4 mg daily for a short-term in patients with and without ED at baseline that was diagnosed using self reports in the treatment of BPH. After 6 weeks of treatment, there was a clinically and statistically significant decrease in total IPSS, QoL and Q_{max} in both groups over baseline. In the non-ED group, the improvements of BPH symptoms were better than in the ED group. However, the only significant improvement that was detected for QoL exists when the two groups were compared with each other. The QoL had decreased by 1.0 point compared with the baseline in patients with ED, whereas in non-ED group, it decreased by 1.9 points. This result was consistent with previous studies findings of significant reductions in total IPSS and QoL, and substantial increases in

Table 2. Mean and percentage change from baseline of efficacy parameters with doxazosin treatment.

	Group I change from baseline (%)	Group II change from baseline (%)	*P*-value**
$IPSS_{total}$	−6.9 ± 6.4 (39.7)*	−8.3 ± 5.8 (46.4)*	0.568
QoL	−1.0 ± 1.8 (23.6)*	−1.9 ± 1.1 (50.6)*	0.018
Q_{max} (mL s^{-1})	2.3 ± 3.3 (22.4)*	3.7 ± 5.3 (32.7)*	0.650
AFR (mL s^{-1})	1.1 ± 1.7 (24.9)*	1.5 ± 2.7 (34.7)*	0.729
IIEF-EF	2.4 ± 6.0*	−1.9 ± 7.2	0.017
IIEF-OF	0.2 ± 2.5	−0.3 ± 2.4	0.451
IIEF-SD	0.2 ± 2.1	−0.3 ± 1.2	0.234
IIEF-IS	1.0 ± 3.8	−0.7 ± 3.1	0.080
IIEF-OS	0.6 ± 2.1	0.5 ± 2.2	0.763

Abbreviations: AFR, average flow rate; IPSS, International Prostate Symptom Score; IIEF-EF, International Index of Erectile Function-Erectile Function; IIEF-IS, International Index of Erectile Function-Intercourse Satisfaction; IIEF-OF, International Index of Erectile Function-Orgasmic Function; IIEF-OS, International Index of Erectile Function-Overall Satisfaction; IIEF-SD, International Index of Erectile Function-Sexual Desire; Q_{max}, maximum flow rate; QoL, quality of life.

Statistical significance within groups (Wilcoxon signed-rank test): *$P < 0.001$, compared with baseline.

**Statistical significance between groups (Mann–Whitney *U*-test);

Q_{max} with doxazosin [7, 8]. In both studies, the α1-adrenoceptor antagonists improved symptom scores by 35%–40% *vs*. baseline and Q_{max} by 16%–26% *vs*. baseline for 3 months of treatment. As shown in our study, doxazosin produced significant improvements at the sixth week of treatment. Our results are similar to Kirby *et al.* [7] who reported an analysis of double-blind trials of the efficacy and tolerability of doxazosin. In that study, although the differences between the mean changes of IPSS and Q_{max} in doxazosin groups and placebo were significant, the mean change in placebo group over baseline was also significant.

The improvements of urinary symptoms and Q_{max} were better in BPH patients without ED than in those with ED at baseline. BPH and ED share a common pathophysiology. Both clinical entities are closely associated with systemic and local factors. It has been shown that an association between manifestations of atherosclerotic disease, for example, non-insulin-dependent diabetes mellitus, hypertension or dyslipidemia, may underlie BPH considering the fact that pathophysiology might be systemic rather than local [9, 10]. In addition, McVary [11] has proposed four leading theories supporting biological plausibility that currently exist, namely, the nitric oxide synthase/NO theory; the autonomic hyperactivity and metabolic syndrome hypothesis; the Rho-kinase activation/endothelin pathway; and pelvic atherosclerosis. Berger *et al.* [12] supported one of these theories that showed the relationship between an age-related impairment of blood supply to the lower urinary tract and pathogenesis of BPH. Although we did not evaluate ED patients for pelvic and penile vascular structures, there might be more severe vascular damage in patients with BPH and ED than without ED. These abovementioned factors may contribute to the improvement of voiding symptoms and Q_{max} in patients with BPH and without ED at baseline.

Our results confirmed the efficacy of doxazosin on erectile functions in BPH patients with and without ED at baseline. We report here that treatment with doxazosin produced significant improvements in IIEF-EF domains in patients with BPH and sexual dysfunction at baseline. In a multicentre study conducted by Kirby *et al.* [7], it has been shown that doxazosin improved sexual functions and produced a significant increase in all domains of the IIEF in patients with BPH and sexual dysfunction at baseline. In that trial, the efficacy of doxazosin-standard and doxazosin-extended release forms in patients with BPH after 13 weeks of treatment were compared. Although the mean changes of all IIEF domain scores were not statistically significant in all patients who were treated with doxazosin-standard, the improvements were considerable in all domains of IIEF in patients with BPH and sexual dysfunction at baseline. The result of mean changes of IIEF-EF domain scores in patients with ED at baseline is consistent with our study. In our study, we evaluate the effects of doxazosin treatment on all domains of IIEF; however, only significant improvements were detected in IIEF-EF domain. The difference is probably because of the duration of treatment period and differences of the study population.

In another multicentre study of 102 patients with BPH, the effects of doxazosin treatment on sexual function were evaluated after 3 months; 80 patients with sexual dysfunction were stratified using IIEF scores into three subgroups according to their degree of ED (severe, moderate or mild) [13]. After 1 month of therapy with doxazosin, there was a significant improvement from baseline in IIEF, which was more evident in the groups entering the study with severe and moderate ED. Our results were also consistent with this study. In our study, the improvements of IIEF-EF domain scores were more evident in patients with severe ED.

Two mechanisms have been proposed to explain patients' improved sexual functioning after treatment for LUTS with α-blockers. First, as the symptoms become less bothersome, patients may feel less 'disabled' by their urinary symptoms and may thus be better able to enjoy other facets of life without feeling inhibited or limited. Alternatively, inhibition of the α1- and α1D-adrenoceptor subtypes that predominate in cavernosal smooth muscle should facilitate erection [14]. Kirby *et al.* [7] stated that α-1-receptor antagonists might improve erectile function in BPH patients with sexual dysfunction. Blockage of α1-receptors that predominate in cavernosal tissues might be responsible for this therapeutic effect. In addition, the relaxation effects of doxazosin have been shown on cavernosal smooth muscle tissue in experimental studies [15]. In our previous study, we established that doxazosin caused concentration-dependent relaxation on corpus cavernosum smooth muscle cells precontracted by phenylephrine that were obtained from patients who underwent penile prosthesis implantation [16]. Also with doxazosin, significantly higher relaxation responses were reached in tissues obtained from patients with BPH.

In our study, we showed that QoL scores significantly improved in patients with BPH and non-ED at baseline ($P = 0.018$). The improvements of QoL may be related to improving the voiding symptoms in that group. It has been known that sexual dysfunction strongly affects QoL, even in advanced age. It was shown that men with ED had significantly lower scores in physical functioning, mental health, emotional function, vitality and general health than in men without ED [17]. In addition, it has been reported that decreased sexual activity due to erection difficulties is a major distress for LUTS patients and has an impact on the LUTS patients' QoL [18]. LUTS patients with ED reported depression, frustration and a loss in self-confidence. In addition, the patients experienced the loss in erectile capacity as a negative influence on the relationship with their partner [18]. Data from a recent placebo-controlled and an open-label study established that successful ED treatment with PDE5 inhibitor notably improved self-esteem, confidence and relationships [19].

In addition, early clinical trials suggest a consistent improvement in IPSS scores with PDE5 inhibitor therapy in men presenting with ED or LUTS [20]. Also Kaplan *et al*. [21] recently reported on the results of a pilot study designed to ascertain the safety and efficacy of the combination of an α-blocker, alfuzosin SR (Uroxatral; Sanofi-Aventis, Bridgewater, NJ, USA), and sildenafil (Viagra; Pfizer Inc, NY, USA) versus monotherapy in the treatment of LUTS and sexual dysfunction. Improvements at 12 weeks in IPSS, Q_{max}, frequency, nocturia and IIEF were significant for all three groups, but greatest for the combination group. As mentioned above, the involvement of the NO/cGMP/PDE pathway in the regulation of lower urinary tract smooth muscle activity might have a role in this association. PDE5 is also expressed in the prostate and bladder and PDE5 inhibitors have been shown to relax precontracted muscle strips from these organs. It has also been shown that, DA-8159, a selective PDE5 inhibitor, significantly lowers the urethral pressure associated with BPH by dilatating the prostate [22]. These findings might explain the improvements in IPSS/LUTS with PDE5 therapy. However, large-scale, placebo-controlled studies are needed to further elucidate the role of PDE5 inhibitor therapy on BPH/LUTS.

The duration of this study was 6 weeks, whereas previous studies have been conducted for 12 weeks or more [7, 23]. A 6-week treatment period was employed in this study, as we wanted to examine the rapid response of the drugs and to prevent a high number of discontinuation. A 6-week treatment phase was also employed in previous studies. They were able to observe the improvement of IPSS and Q_{max} scores in a 6-week treatment phase or in an even shorter period (4 weeks) [24].

Treatment with doxazosin was well tolerated and serious adverse events causing the discontinuation of the treatment were not seen during the treatment course in both groups.

In our study, we also showed that the prevalence of self-reported ED in BPH patients is lower than the true prevalence of ED. Thus, 58.5% of those with self-reported ED were subsequently found not to meet the criteria for ED using the IIEF instrument and 46% of those, who by self-report did not have ED, were subsequently found to have mild to severe ED using the IIEF assessment. We suggest that comorbidities, especially BPH, educational level, sociocultural and socioeconomic factors might be the major factors contributing to the discrepancy in the prevalence in self-reported ED and IIEF-EF-defined ED in these patients. Our results were concordant with the previous study that of Wu *et al.* [25]. They suggested that estimates of ED prevalence in the general population should not rely on self-reporting alone, because it is likely to underestimate the true prevalence of ED [25]. We recommend that patients with LUTS should be questioned for ED using IIEF. The IIEF is a useful tool and is helpful for follow-up of a patient to evaluate the affects and efficacy of treatments for erectile functions.

In conclusion, however not controlled with placebo, doxazosin is effective in reducing the clinical symptoms of BPH and improving Q_{max} in patients with and without ED. Doxazosin improves erectile functions in BPH patients having ED at baseline. The improvements of IIEF-EF domain score is more evident in patients with severe ED. Future larger studies are needed for clearly understanding the effects of α-blocker therapy on BPH patients who have sexual dysfunction at baseline. In addition, we recommend that patients who are admitted to urology outpatient clinics with complaints of LUTS should be questioned for ED using IIEF form even if they reports normal erectile function.

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