



Effect of Alpha-Blockers on Patients with Benign Prostatic Hyperplasia with Inflammatory Cells in the Prostatic Fluid

Yu-Mi Seo, Hyung-Jee Kim

Department of Urology, Dankook University College of Medicine, Cheonan, Korea

Purpose: To determine if alpha-blocker monotherapy is effective on patients with benign prostatic hyperplasia (BPH) and prostatic inflammation.

Materials and Methods: Patients who were admitted for the treatment of lower urinary tract symptoms for 18 months were enrolled in this study. All were subjected to an International Prostate Symptom Score (IPSS) evaluation, prostate specific antigen analysis, urinalysis, residual urine testing, prostate massage, and transrectal prostate ultrasonography. The presence of inflammation in the secretion after the prostate massage was observed at high magnification. Patients with a leukocyte count of more than 15 were diagnosed as positive and classified as group 1 (experimental group), whereas those with a leukocyte count of less than 15 were diagnosed as negative and classified as group 2 (control group). Silodosin was administered (4 mg twice a day for two months).

Results: Group 1: After one and two months, there was no significant difference in the maximum urinary flow rate (Qmax) and post-void residual volume (PVR) compared to the baseline. The total IPSS was significantly improved over the 8-week study period. All symptoms except for Qmax and PVR showed significant improvement in the second month. Group 2: After one and two months, significant improvement was observed in all domains of the IPSS, and Qmax and PVR assessment, except for the PVR at one month.

Conclusions: In patients with BPH who have not been treated properly, other treatments based on prostatitis may be needed in addition to alpha blockers if there is inflammation on expressed secretion of prostate.

Keywords: Prostate; Inflammation; Adrenergic alpha-antagonists

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Correspondence to: Hyung-Jee Kim

<http://orcid.org/0000-0002-7993-1881>

Department of Urology, Dankook University Hospital, 201 Manghyang-ro, Dongnam-gu, Cheonan 31116, Korea

Tel: +82-41-550-6630, Fax: +82-41-556-7060

E-mail: killtumor@dankook.ac.kr

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common disease in older men [1]. Four out of five middle-aged or elderly men have lower urinary tract symptoms (LUTS) that make their daily life difficult and lower their quality of life (QoL) [2].

Recently, significant changes have been made in the

treatment of BPH; however, surgery remains the treatment of choice for complications of BPH, such as recurrent urinary retention, renal failure, bladder stones, and recurrent urinary tract infections. Nevertheless, the number of prostate surgeries is declining globally [3]. Medical therapy based on the patient's preference has become more common for patients with LUTS.

Medical therapy for the treatment of BPH with 5-alpha-

reductase inhibitors and alpha-blockers can improve the LUTS and QoL of men with BPH. Of these, alpha-blockers are the most common and important medicines for reducing the resistance of the bladder outlet.

On the other hand, prostatitis can often occur in patients with BPH. Prostatitis is the most common urological disease with a reported of 5-9% of adult men [4,5]. In Korea, approximately 15-25% of patients who visited urology clinics are estimated to be patients with prostatitis syndrome [6,7]. In addition, some 5-20% of the patients with BPH have prostatitis symptoms, such as pelvic pain and painful ejaculation, and the histologic and microbiologic findings may show a similar pattern between the two diseases [8,9].

Few studies have evaluated prostatitis in patients with BPH. Theoretically, prostatitis can be assessed indirectly based on the presence of calcification or the infiltration of inflammatory cells in the prostate gland [9,10]. Generally, if there are no serious complications and LUTS are not severe in patients with BPH and prostatitis, only treatment for BPH would be performed. On the other hand, because of the difficulty in making an accurate differentiation of LUTS/BPH from LUTS/prostatitis, it is necessary to evaluate the clinical significance of the accompanying prostatitis in patients with BPH. Therefore, this study examined whether alpha-blocker monotherapy is effective on patients with BPH and prostatic inflammation.

MATERIALS AND METHODS

Patients, who were admitted to the urology clinic for the treatment of LUTS for 18 months after Institutional Review Board (IRB) screening, were included in the study. The study was reviewed and approved by the IRB of Dankook University Hospital (IRB no. DKUH 2012-03-018-009). This was a randomized single-blind study. The patients were aged ≥ 50 years, were outpatients, and had LUTS/BPH. The inclusion criteria were a total International Prostate Symptom Score (IPSS) ≥ 8 , QoL score ≥ 3 , prostate volume (measured by transrectal ultrasonography) ≥ 20 ml, maximum urinary flow rate (Qmax) < 15 ml/sec with a voided volume ≥ 150 ml, and a post-void residual volume (PVR) < 150 ml. Patients who underwent prostate surgery and patients with urinary tract infections, neurogenic bladder, prostate cancer, bladder stones, or indwelling urethral catheters were excluded. All patients were subjected to an IPSS evaluation,

prostate-specific antigen analysis, urinalysis, residual urine testing, prostate massage, and transrectal prostate ultrasonography. The presence or absence of inflammation in the secretion obtained after prostate massage was observed at a high magnification ($\times 400$). Patients with a leukocyte count of more than 15 were diagnosed as positive and classified as group 1 (experimental group), whereas those with a leukocyte count of less than 15 were diagnosed as negative and classified as group 2 (control group). Silodosin was administered (4 mg twice a day for two months). The effect was investigated by IPSS, Qmax, and PVR assessment before and after administration. Each group was subjected to these tests one month later, and were repeated two months later. IPSS items 1, 3, 5, and 6 were classified as voiding symptoms, whereas items 2, 4, and 7 were classified as items with storage symptoms. The primary endpoints were changes in symptoms measured by the IPSS at the baseline and one and two months after the silodosin treatment. The secondary endpoints were changes in the study measured by Qmax and PVR at the baseline and one and two months after treatment, which included the use of silodosin to treat LUTS/BPH with prostatitis-like symptoms. The Qmax was analyzed using Dantec Urolyn 1000 flowmeter (Dantec, Skovlunde, Denmark), and the PVR was measured using BladderScanTM (Diagnostic Ultrasound Corporation, Bothell, WA, USA).

Statistical significance was assessed using a Student's t-test and paired t-test, and $p < 0.05$ was considered significant.

RESULTS

A total of 41 patients were included in the study. Group 1 (experimental group) contained 23 men with prostatitis and group 2 (control group) contained 18 men without prostatitis.

1. All Patients

The mean age of the patients was 68.6 ± 6.4 years old. The mean serum prostate-specific antigen (PSA) level of the patients was 1.6 ± 1.3 mg/dl. The patients were excluded from the possibility of prostate cancer when the PSA level was 4.0 mg/dl or more. The mean size of the prostate of the patients was 33.8 ± 10.6 g. The mean Qmax of the patients was 10.8 ± 4.1 ml/sec. The mean PVR of the patients was 55.5 ± 51.2 ml. All patients fulfilled the criteria. The

Qmax in the first month was 12.5 ± 6.3 ml/sec ($p=0.051$). No significant difference compared to the baseline was noted; however, the PVR was 48.1 ± 44.8 ml ($p=0.041$). On the other hand, the Qmax and PVR after two months were 13.0 ± 4.8 ml/sec ($p=0.003$) and 44.2 ± 33.0 ml ($p=0.003$), respectively.

The total IPSS was improved significantly over the 8-week study period. In addition, each period showed significant improvement compared to the previous period.

The changes in urination, storage symptoms, and QoL of IPSS were similar to the changes in the total score. The domain score was improved significantly over the 8-week follow-up period. Furthermore, all symptoms showed significant improvement in the second month compared to the first month (Table 1).

2. Group 1 Patients (Experimental Group)

The mean age was 68.9 ± 7.0 years old. The serum PSA level was 1.8 ± 1.2 mg/dl. The mean size of the prostate was 36.5 ± 12.8 g. The mean Qmax was 10.6 ± 2.6 ml/sec. The mean PVR of the patients was 41.3 ± 44.1 ml. The Qmax was 12.3 ± 5.6 ml/sec ($p=0.117$), and the PVR was

41.5 ± 36.4 ml ($p=0.981$) in the first month. No significant difference compared to the baseline was observed. After two months, the Qmax was 12.1 ± 4.5 ml/sec ($p=0.083$), and the PVR was 46.8 ± 31.8 ml ($p=0.841$).

The total IPSS was not improved significantly in the first month but was improved significantly over the 8-week study period. All symptoms except for the Qmax and PVR showed significant improvement in the second month compared to the first month. The changes in urination, storage symptoms, and QoL of IPSS were similar to the changes in the total score (Table 2).

3. Group 2 Patients (Control Group)

The mean age of the control group patients was 68.4 ± 5.7 years. No significant difference compared to the group 1 patients was noted ($p=0.924$). The serum PSA level was 1.4 ± 1.3 mg/dl. The mean size of the prostate was 30.2 ± 5.6 g. The mean Qmax was 11.1 ± 5.5 ml/sec, and the mean PVR was 63.6 ± 55.1 ml; there was no significant difference compared to the group 1 patients ($p=0.424$, 0.06, 0.999, and 0.53, respectively). In the first month, the Qmax was 14.4 ± 7.0 ml/sec ($p=0.042$), and the PVR was 56.1 ± 53.4

Table 1. Changes in the International Prostate Symptom Score (IPSS) of all patients

	Baseline	First month	Second month	p-value ^{a)}	p-value ^{b)}	p-value ^{c)}
IPSS, total	20.1 ± 6.7	16.7 ± 7.6	13.1 ± 6.9	0.034	0.001	0.001
IPSS, voiding symptom	12.7 ± 4.7	9.8 ± 5.0	7.2 ± 4.5	0.033	0.001	0.001
IPSS, storage symptom	8.0 ± 3.3	6.9 ± 3.4	5.7 ± 3.2	0.047	0.001	0.002
IPSS, quality of life	4.5 ± 1.1	3.9 ± 1.3	3.2 ± 1.2	0.005	0.001	0.001
Qmax (ml/sec)	10.8 ± 4.1	12.5 ± 6.3	13.0 ± 4.8			
PVR (ml)	55.5 ± 51.2	48.1 ± 44.8	44.2 ± 33.0			

Values are presented as mean \pm standard deviation.

Qmax: maximum urinary flow rate, PVR: post-void residual volume.

^{a)}p-value compared baseline to the first month.

^{b)}p-value compared baseline to the second month.

^{c)}p-value compared first month to the second month.

Table 2. Changes in the International Prostate Symptom Score (IPSS) of the experimental group (group 1)

	Baseline	First month	Second month	p-value ^{a)}	p-value ^{b)}	p-value ^{c)}
IPSS, total	20.7 ± 7.6	17.9 ± 7.5	14.6 ± 7.0	0.228	0.001	0.011
IPSS, voiding symptom	12.2 ± 5.1	10.2 ± 4.7	7.9 ± 4.5	0.05	0.001	0.027
IPSS, storage symptom	8.3 ± 3.5	7.7 ± 3.5	6.3 ± 3.4	0.258	0.011	0.011
IPSS, quality of life	4.6 ± 1.1	4.3 ± 1.2	3.6 ± 1.1	0.367	0.001	0.024
Qmax (ml/sec)	10.6 ± 2.6	12.3 ± 5.6	12.1 ± 4.5			
PVR (ml)	41.3 ± 44.1	41.5 ± 36.4	46.8 ± 31.8			

Values are presented as mean \pm standard deviation.

Qmax: maximum urinary flow rate, PVR: post-void residual volume.

^{a)}p-value compared baseline to the first month.

^{b)}p-value compared baseline to the second month.

^{c)}p-value compared first month to the second month.

Table 3. Changes in the International Prostate Symptom Score (IPSS) of the control group (group 2)

	Baseline	First month	Second month	p-value ^{a)}	p-value ^{b)}	p-value ^{c)}
IPSS, total	19.3±5.4	15.2±7.7	10.6±6.2	0.009	0.001	0.004
IPSS, voiding symptom	11.7±4.3	9.3±5.3	5.9±4.3	0.006	0.001	0.003
IPSS, storage symptom	7.6±3.2	5.9±3.0	4.7±2.5	0.039	0.002	0.025
IPSS, quality of life	4.3±1.1	3.4±1.3	2.6±1.0	0.002	0.002	0.006
Qmax (ml/sec)	11.1±5.5	14.4±7.0	14.3±5.1			
PVR (ml)	63.6±55.1	56.1±53.4	40.1±35.6			

Values are presented as mean±standard deviation.

Qmax: maximum urinary flow rate, PVR: post-void residual volume.

^{a)}p-value compared baseline to the first month.

^{b)}p-value compared baseline to the second month.

^{c)}p-value compared first month to the second month.

ml ($p=0.130$). After two months, however, there was significant improvement in the Qmax and PVR. The Qmax was 14.3 ± 5.1 ml/sec ($p=0.001$), and the PVR was 40.1 ± 35.6 ml ($p=0.007$).

The total IPSS was improved significantly over the 8-week study period and was similar to that of the total patient group. Furthermore, each period showed significant improvement compared to the previous period.

The changes in urination, storage symptoms, and QoL of IPSS were similar to the changes in the total score and total patient group. The domain score was improved significantly over the 8-week follow-up period. In addition, all symptoms except for Qmax showed significant improvement in the second month compared to the first month (Table 3).

DISCUSSION

The medical treatment of BPH largely involves alpha-blockers acting on the dynamic component and 5-alpha-reductase inhibitors acting on the static component of the prostate. On the other hand, only the voiding portion of LUTS/BPH is usually considered. Some patients with BPH have prostatitis-like symptoms, such as pelvic, suprapubic, or perineal pain and painful ejaculation [8]. BPH and prostatitis are likely to coexist in aging men. Recently, a study reported that 57.2% of men with prostatitis had a history of BPH, and 38.7% of men with BPH had a history of prostatitis [11]. Another study reported that men with a history of prostatitis were twice as likely to have a history of BPH and significantly higher scores on the American Urological Association Symptom Index [12]. In addition, approximately 20% of patients with LUTS

suggestive of BPH had pain or discomfort on ejaculation. These men had more severe LUTS, greater difficulty, and a higher prevalence of sexual dysfunction than those without the symptoms indicative of prostatitis [13].

As chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is an important multifactorial problem that affects men of all ages and demographic subgroups, patients with CP/CPPS are candidates for many experimental therapies. The three most common medications prescribed by physicians are antimicrobial agents, anti-inflammatory medicines, and alpha-adrenergic receptors antagonists [14]. Among these medications, the effects of alpha-blockers on BPH and prostatitis overlap. Many theories to explain the efficacy of the medicines prescribed have been proposed. Nevertheless, although the effects of alpha-blockers on BPH have been demonstrated, the effects of alpha-blockers on prostatitis are clear [15]. Recently, the efficacy of alfuzosin showed improvements in the National Institutes of Health chronic prostatitis symptom index (NIH-CPSI) and IPSS total score. In particular, voiding factors were improved significantly in relation to the NIH-CPSI and IPSS scores in the alfuzosin treatment group [16]. Alpha blockers are an important tool in the physician's armamentarium for the treatment of CP/CPPS [17]. On the other hand, few studies examined the improvement of urinary symptoms in BPH patients with pain but only through alpha-blockers monotherapy. Empirical therapy with antibiotics in BPH patients with symptoms of prostatitis does not appear to be correct because it involves a range of problems, such as the expression of antibiotic resistant bacteria. Silodosin is effective in patients with LUTS/BPH and there was no significant difference in the efficacy of silodosin and tamsulosin when comparing silodosin 8 mg, tamsulosin 0.4

mg, and a placebo [18]. Silodosin 4 mg was associated with a significant reduction of NIH-CPSI in patients with CP/CPPS [19]. In this study, when alpha blocker monotherapy was administered, the mean Qmax and mean residual urine were similar between the base and at 2 months in BPH patients with inflammation. In addition, in patients reported that none of the domains of IPSS showed any changes until 4 weeks, but it was improved significantly at 8 weeks compared to the base of the study. This suggests that an alpha-blocker alone does not have an objective effect on the treatment of BPH patients with inflammation compared to the control group, but symptomatic improvement can be seen.

Other treatment modalities for prostatitis besides alpha-blockers may be required for the treatment of BPH patients with inflammation. On the other hand, because patients treated with other urological services were excluded, the results of the present study may not applicable to patients with LUTS/BPH or LUTS/prostatitis who have urinary tract problems. Furthermore, this study using only silodosin may not produce the same results as other alpha-blockers.

CONCLUSIONS

In patients with BPH, who have not been treated properly, other treatments based on prostatitis may be needed in addition to alpha blockers if there is any inflammation on expressed secretion of prostate.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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