

Infection/Inflammation

The Effect of Intraprostatic Chronic Inflammation on Benign Prostatic Hyperplasia Treatment

Young Kee Kwon, Mi Sun Choe¹, Kyung Won Seo, Chol Hee Park, Hyuk Soo Chang, Byung Hoon Kim, Chun Il Kim

Departments of Urology and ¹Pathology, Keimyung University School of Medicine, Daegu, Korea

Purpose: Asymptomatic chronic inflammation of the prostate is a common finding in benign prostatic hyperplasia (BPH). We investigated how the chronic inflammation affects medical treatment for BPH.

Materials and Methods: One pathologist reviewed the chronic inflammation of 82 BPH patients who underwent transrectal ultrasonography (TRUS)-guided needle biopsy. The extent of chronic inflammation was classified into 4 grades, categorized into two groups: the low-grade group and the high-grade group. We compared total, voiding, and storage International Prostate Symptom Score (IPSS) and quality of life (QoL) between the groups at baseline and 1, 3, 6, and 12 months after medical treatment for BPH.

Results: There were no significant differences in total IPSS or QoL between the groups during the follow-up period. The low-grade group showed continuous improvement of storage symptoms until 12 months; however, the high-grade group showed improvement until 3 months. Maximal improvements of QoL were observed at 6 months in the high-grade group and at 3 months in the low-grade group. There was no episode of surgery in the low-grade group, but four patients in the high-grade group (9.1%) underwent surgical treatment due to acute urinary retention or insufficient therapeutic response.

Conclusions: Although there was no statistical significance, improvements in IPSS were higher and lasted longer in the low-grade group. We might suggest medical treatment for intraprostatic chronic inflammation in BPH patients.

Key Words: *Diagnosis; Inflammation; Prostatic hyperplasia*

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Corresponding Author:

Chun Il Kim
Department of Urology, Dongsan
Medical Center, Keimyung University
School of Medicine, 194,
Dongsan-dong, Jung-gu, Deagu
700-712, Korea
TEL: +82-53-250-7646
FAX: +82-53-250-7643
E-mail: cikim@dsmc.or.kr

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive disease that causes lower urinary tract symptoms (LUTS), causes acute urinary retention (AUR), or leads to BPH-related surgery, and it greatly affects quality of life (QoL) [1,2]. It has also been reported that intraprostatic inflammation frequently accompanies BPH and accelerates the pathogenesis and progression of this condition [3-7]. Acute intraprostatic inflammation causes symptoms that can be easily treated. However, many cases of chronic intraprostatic inflammation go untreated because the condition has no symptoms.

We conducted this study to identify the effects of intraprostatic inflammation on therapeutic results in patients who receive medical treatment for BPH.

MATERIALS AND METHODS

This study retrospectively analyzed the medical records of 82 patients with abnormal prostate-specific antigen (PSA) and digital rectal examination results who were diagnosed with prostatic hyperplasia by biopsy and who had received drug treatment with alpha-adrenergic blockers (α -blockers) and 5-alpha reductase inhibitors between September 2005 and June 2008. The study analyzed patients who could be followed up for six months or longer. Patients with urinary tract infection, prostate cancer, urethral stricture, or neurogenic bladder and patients who underwent BPH-related surgery were excluded from the study.

One pathologist reviewed the intraprostatic inflammation of 82 patients. The extent of intraprostatic inflammation was classified on the basis of the four-point scale proposed by Irani et al [8]. This scale includes four grades:

grade 0 (no inflammatory cells), grade I (scattered inflammatory cell infiltrate within the stroma without lymphoid nodules), grade II (nonconfluent lymphoid nodules), and grade III (large inflammatory areas with confluence of infiltrate).

The subjects were then divided into the low-grade group (grades 0 and I), which consisted of 38 cases (46%), and the high-grade group (grades II and III) of 44 cases (54%). The International Prostate Symptom Score (IPSS) and QoL of the groups before treatment and at 1, 3, 6, and 12 months of treatment, as well whether they had undergone surgery, were compared so as to identify the effects of intraprostatic inflammation on the medical treatment of BPH. Statistical analysis was performed by using Student's t-test and ANOVA test of SPSS, version 12.0. p-values < 0.05 were considered statistically significant.

RESULTS

A total of 6, 32, 35, and 9 patients had grade 0, I, II, and III inflammation. The prostate volume of 38 cases in the low-grade group (46%) and 44 cases in the high-grade group

(54%) before treatment were 51.0±3.64 ml and 64.0±5.47 ml (p=0.073), respectively; PSA values were 7.9±1.14 ng/ml and 9.0±1.20 ng/ml (p=0.506), respectively; IPSS were 19.9± 1.98 and 18.1±1.22 (p=0.468), respectively; and QoL scores were 4.1±0.27 and 3.6±0.19 (p=0.108), respectively (Table 1).

The improvements of IPSS at 1, 3, 6, and 12 months of treatment were -6.7±2.02, -8.2±2.14, -10.2±1.92, and -9.7±1.70, respectively in the low-grade group, and -5.0± 1.24, -6.7±1.45, -6.7±1.65, and -6.3±1.57, respectively, in the high-grade group. All the improvements compared with IPSS before treatment were statistically significant, but there was no significant difference in improvement between the two groups (p=0.463, p=0.558, p=0.174, and p=0.146, respectively). Compared with previous total IPSS, there were significant improvements in the low-grade group until 6 months (1 month vs. 3 month, 3 months vs. 6 months: p=0.04, p=0.04) (Table 2). Both groups showed the highest improvements at 6 months of drug treatment, but the improvement in the low-grade group was 3.5 points higher than that of the high-grade group, which was the

TABLE 1. Baseline values of the low- and high-grade groups before treatment

IPSS	Baseline values of the groups before treatment (n)		
	Low grade (38)	High grade (44)	p-value
IPSS			
Storage	8.1±0.97	7.3±0.49	0.446
Voiding	11.8±1.36	10.8±0.96	0.539
Total	19.9±1.98	18.1±1.22	0.468
QoL	4.1±0.27	3.6±0.19	0.108
Prostate volume (ml)	51.0±3.64	64.0±5.47	0.073
PSA (ng/ml)	7.9±1.14	9.0±1.20	0.506
Age (years)	62.9±8.12	66.0±4.99	0.125

Low grade: chronic inflammation grade 0, I, High grade: chronic inflammation grade II, III, IPSS: international prostate symptom score, QoL: quality of life, PSA: prostate-specific antigen

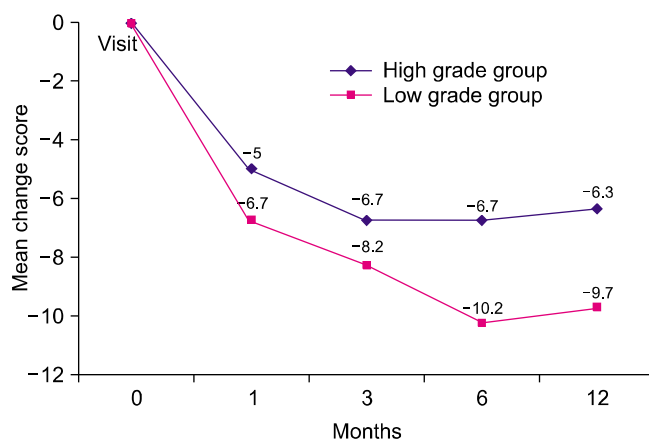


FIG. 1. Mean changes in total IPSS during 12 months. IPSS: International Prostate Symptom Score, High-grade group: chronic inflammation grades II and III, Low-grade group: chronic inflammation grades 0 and I. The improvement of IPSS in the low-grade group was higher and longer for 12 months.

TABLE 2. Mean changes from baseline in the low- and high-grade groups after treatment

		Mean changes over baseline of the groups after treatment (n)			
		1 month (82)	3 months (82)	6 months (82)	12 months (78) ^a
		Low vs. High	Low vs. High	Low vs. High	Low vs. High
IPSS	Storage	-2.5 ^c vs. -2.2 ^{b,c}	-3.2 ^c vs. -2.4 ^{b,c}	-3.9 ^c vs. -2.3 ^{b,c}	-4.0 ^c vs. -2.1 ^{b,c}
	Voiding	-4.2 ^c vs. -2.8 ^{b,c}	-5.0 ^c vs. -4.3 ^{b,c}	-6.3 ^{c,d} vs. -4.4 ^{b,c}	-5.7 ^c vs. -4.2 ^{b,c}
	Total	-6.7 ^c vs. -5.0 ^{b,c}	-8.2 ^{c,d} vs. -6.7 ^{b,c}	-10.2 ^{c,d} vs. -6.7 ^{b,c}	-9.7 ^c vs. -6.3 ^{b,c}
QoL		-0.6 ^c vs. -0.3 ^{b,c}	-1.1 ^c vs. -0.6 ^{b,c}	-1.0 ^c vs. -0.9 ^{b,c}	-0.8 ^c vs. -0.7 ^{b,c}

Low: low grade group (chronic inflammation grade 0, I), High: high grade group (chronic inflammation grade II, III), IPSS: international prostate symptom score, QoL: quality of life, PSA: prostate-specific antigen, ^a: 4 cases received transurethral resection of the prostate, ^b: p-value (> 0.05) of between low & high grade groups (independent t-test), ^c: p < 0.05 vs. baseline; statistical significance within groups (paired t-test), ^d: p < 0.05 vs. previous IPSS (except baseline); statistical significance within groups (ANOVA test)

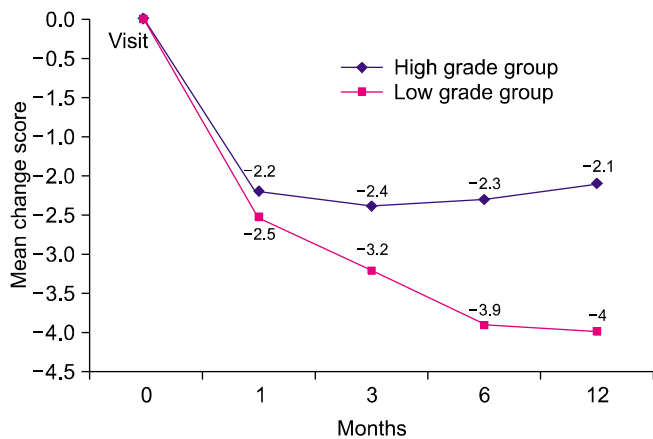


FIG. 2. Mean changes in storage symptom score during 12 months. High-grade group: chronic inflammation grades II and III, Low-grade group: chronic inflammation grades 0 and I. The low-grade group showed continuous improvement of storage symptoms until 12 months; however, the high-grade group showed improvement until 3 months.

greatest difference during the treatment period (Fig. 1). The changes in storage symptoms at 1, 3, 6, and 12 months of treatment were -2.5 ± 0.96 , -3.2 ± 0.95 , -3.9 ± 0.92 , and -4.0 ± 0.92 , respectively, in the low-grade group, and -2.2 ± 0.53 , -2.4 ± 0.53 , -2.3 ± 0.60 , and -2.1 ± 0.55 , respectively, in the high-grade group. The low-grade group showed continuous improvement until 12 months of drug treatment, whereas the improvement of the high-grade group tended to decrease after 3 months (Fig. 2).

The improvement in QoL relative to before treatment was significant in both groups. The low-grade group showed improvements of -0.6 ± 0.28 , -1.1 ± 0.30 , -1.0 ± 0.31 , and -0.8 ± 0.31 at 1, 3, 6, and 12 months of treatment, respectively, and the high-grade group showed improvements of -0.3 ± 0.17 , -0.6 ± 0.26 , -0.9 ± 0.26 , and -0.7 ± 0.27 , respectively. There was no significant difference between the two groups ($p=0.362$, $p=0.309$, $p=0.846$, and $p=0.701$, respectively). However, it took 3 months of treatment before the low-grade group showed its highest improvement in QoL and 6 months for the high-grade group (Table 2, Fig. 3). Four cases from the high-grade group underwent prostate surgery after six months of drug treatment.

DISCUSSION

Kohnen et al reported that when prostate tissue is removed by surgery from prostatic hyperplasia patients with no symptoms of acute prostatitis, asymptomatic intraprostatic chronic inflammation National Institute of Health (NIH) category IV is observed in 43% to 98% of cases [9]. Nickel et al reported on the basis of the REDuction by DUtasteride of prostate Cancer Events (REDUCE) study that chronic inflammation is observed in 77.6% of patients with lower urinary tract symptoms and that the higher the average chronic inflammation score, the higher the IPSS

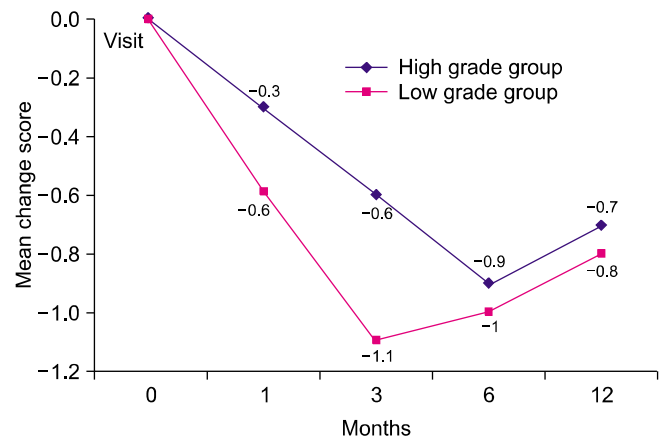


FIG. 3. Mean changes in QoL score during 12 months. QoL: quality of life, High-grade group: chronic inflammation grades II and III, Low-grade group: chronic inflammation grades 0 and I. Maximal improvements of QoL were observed at 6 months in the high-grade group and at 3 months in the low-grade group.

[10]. In their studies on the correlation between intraprostatic chronic inflammation and BPH, Roehrborn et al and Nickel et al claimed that intraprostatic chronic inflammation affects the progression of prostatic hyperplasia [3,11]. Mishra et al also insisted that asymptomatic intraprostatic chronic inflammation can affect BPH progression and acute urinary retention [4-6]. However, there are still no clinical studies of the correlation between intraprostatic inflammation and the therapeutic effects of prostatic hyperplasia. Thus, a study on this subject is warranted.

The present study divided prostatic hyperplasia patients into a low-grade group and a high-grade group on the basis of the four-point scale for the extent of intraprostatic inflammation as proposed by Irani et al [8]. We investigated the clinical effects of intraprostatic inflammation on the drug treatment of BPH patients by analyzing the improvements in IPSS and QoL as recorded by the patients themselves at 1, 3, 6, and 12 months of drug treatment. The improvements in IPSS and QoL after drug treatment showed no statistical differences between the two groups, but the improvements of the low-grade group were more continuous and greater than those of the high-grade group during the follow-up period. In particular, compared with previous total IPSS, there were significant improvements in the low-grade group until 6 months (1 month vs. 3 months, 3 months vs. 6 months: $p=0.04$, $p=0.04$), and the improvement in storage symptoms continued for 12 months. Furthermore, it took 3 months until the highest improvement of QoL in the low-grade group was seen, and 6 months in the high-grade group. This shows that the reaction of the low-grade group to drug treatment for prostatic hyperplasia was faster than that of the high-grade group (Fig. 3).

Although Nickel et al reported that the higher the average chronic inflammation score, the higher the IPSS, this study did not find any difference in IPSS or QoL before

treatment between the two groups [10]. The reason for this appears to be that this study performed transrectal ultrasonography-guided needle biopsy (TRUSBx) for patients with high PSA and excluded subjects who had acute urinary retention and those who had undergone BPH-related surgery.

Kang et al compared the effects of drug treatment between two groups who were divided by the existence of prostatitis through prostate massage [12]. They found that those with prostatitis experienced less improvement in storage symptoms from the drug treatment of prostatic hyperplasia than did those with no prostatitis. This was similar to the result of the present study, which divided subjects into two groups according to the extent of intraprostatic inflammation through TRUSBx.

Roehrborn et al and Ha et al reported that more severe intraprostatic inflammation has a greater impact on BPH progression and acute urinary retention [3,7]. Kefi et al also stated that intraprostatic chronic inflammation is a more meaningful factor affecting acute urinary retention than prostate volume, PSA, and age [5]. During the follow-up in our study, one patient underwent transurethral resection of the prostate due to the development of acute urinary retention and three patients underwent the same surgery due to the lack of efficacy of the medication. The intraprostatic inflammation in these patients was all high grade. The mean prostate volume of the patients whose drug treatment had failed was 58.75 ml, the mean IPSS was 19 points, the mean PSA was 4.04 ng/ml, the mean QoL was 3.75, and the mean age was 70.75. Statistical comparison with other patients was not reasonable because of the low number of cases. However, because all the patients who received surgery were in the high-grade group, we could assume that the more severe the inflammation, the higher the possibility of the failure of medical treatment. Even though it is not possible to perform TRUSBx for all patients before drug treatment to find intraprostatic inflammation, we could indirectly infer inflammation by using inflammatory cytokines such as interleukin-6 and interleukin-8, which are involved in intraprostatic inflammation [13-15], or C-reactive protein, which is a nonspecific inflammation factor.

Nickel et al examined the tissues of patients who had undergone transurethral resection of the prostate due to BPH and found the existence of inflammation in all of them but could not find any clinical significance of the asymptomatic category IV chronic prostatitis in BPH as a result of the lack of meaningful correlation between the degree and pattern of inflammation, catheterization, the presence of bacteria, and serum PSA or PSA density [16]. However, Collins et al claimed that prostatitis could be a risk factor in the development of pathological prostatic hyperplasia into clinical prostatic hyperplasia [17] and that chronic intraprostatic inflammation affects the progress of prostatic hyperplasia [10].

Meanwhile, Nickel presented the importance of additional treatment of chronic intraprostatic inflammation by stating that if the symptoms of prostatic hyperplasia were

correlated with intraprostatic inflammation, anti-inflammatory agents would be a new treatment goal for prostatic hyperplasia [18]. It has been reported that IPSS improvements as a result of drug treatment of prostatic hyperplasia were more significant with the combined therapy using an α -blocker and anti-inflammatory agent than with the single therapy using an α -blocker alone [19,20]. Minnery and Getzenberg also reported that the additional use of ibuprofen together with an α -blocker for prostatic hyperplasia patients was more effective in reducing the expression of the JM-27 genes that generate proteins related to prostatic hyperplasia and in improving the symptoms of prostatic hyperplasia [21]. Many similar studies have found that the management of intraprostatic inflammation plays an important role in the improvement of IPSS in the medical treatment of prostatic hyperplasia patients, but studies on intraprostatic inflammation and response to drug treatment are still insufficient due to the lack of confirmation of inflammation before treatment.

This study examined the extent of inflammation through TRUSBx and the changes in IPSS and QoL after drug treatment. This study is meaningful because it identified that the lower the inflammation, the better the response to drug treatment, although there was no statistical significance. We believe that additional treatment of inflammation will be required in drug treatment of BPH in the future, and a large-scale study is necessary to investigate the extent of intraprostatic inflammation and the response to medical treatment of BPH in a larger number of patients.

CONCLUSIONS

Ninety-three percent of BPH patients had chronic inflammation. The differences in IPSS and QoL before and after drug treatment between the two groups divided by the extent of intraprostatic inflammation were not statistically significant. However, the low-grade group experienced greater improvement in IPSS during the treatment period and their storage symptoms improved continuously until 12 months. Furthermore, no patient in the low-grade group underwent BPH-related surgery due to failure of medical treatment for BPH, but four cases in the high-grade group (9.1%) required the surgery. Therefore, we might consider whether more active treatment of intraprostatic inflammation is necessary in the medical treatment of BPH. In the future, clinical studies on the correlation between intraprostatic inflammation and BPH treatment are required, and such studies should include more cases and a longer follow-up period.

Conflicts of Interest

The authors have nothing to disclose.

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