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Clinical Course of the Benign Prostate Hyplasia Patients during the Intermittent Use of 5-Alpha Reductase Inhibitors

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Purpose: 5-Alpha reductase inhibitors (5ARI), inhibit the conversion of testosterone to dihydrotestosterone, which is essential in prostate hyperplasia, and decreases the prostate volume directly. On the other hand, 5ARI have a range of side effects, such as sexual dysfunction. After the discontinuation of 5ARI, prostate regrowth occurs rapidly until it reaches the baseline size. This study examined the effects of 5ARI when used intermittently.

Materials and Methods: Between March 2009 and May 2017, patients who visited one physician's outpatient clinic and were diagnosed with BPH underwent transrectal ultrasonography. The selected patients began to take 5ARI until the prostate size decreased at least 10% of the baseline (the first medication). After confirming adequate prostate shrinkage, the patients stopped medication until prostate regrowth reached 50% of the decreased size. After regrowth, they restarted medication for one year (second medication). The prostate size, serum prostate specific antigen (PSA) levels, international prostate symptom score (IPSS) scores, and maximum flow rate (Qmax) in uroflowmetry were collected after the first and second medication and compared using paired t-tests.

Results: Sixty patients with a mean age of 65.1 years were included in the study. The prostate size and serum PSA level increased after the second medication compared to the first, and the prostate reduction and Qmax in uroflowmetry decreased significantly. On the other hand, the symptoms felt by the patients surveyed by the IPSS scores showed no significant difference.

Conclusions: 5ARI appear to be less effective in reducing the prostate volume and improving uroflowmetry after discontinuation.

Keywords: 5-Alpha reductase inhibitors; Prostatic hyperplasia

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INTRODUCTION

Benign prostate hyperplasia (BPH) is a disease, in which progressive enlargement of the prostate leads to extrinsic compression of the prostate urethra and impaired voiding [1]. Although BPH is not life threatening, various lower urinary symptoms caused by the disease reduce the quality of life of many senile males [2]. BPH treatments aim to alleviate the urination problems, prevent disease progression, and improve the quality of life [3]. Alpha-adrenergic receptor antagonists (α-blockers) and 5-alpha reductase inhibitors (5ARI) are the most common medical treatments in patients with BPH.

5ARI inhibit the conversion of testosterone to dihydro-

testosterone, which is essential in prostate hyperplasia, and decrease the prostate size directly, leading to an alleviation of the lower urinary tract symptoms (LUTS) [4]. On the other hand, 5ARI have a range of adverse effects, such as sexual dysfunction and mood disorder, which can reduce the patients' compliance [5]. After discontinuing 5ARI, the prostate volume recovers to the size of pre-medication, and requires re-dosing [6]. Therefore, some urologists repeat the prescription and discontinuation of 5ARI intermittently to reduce the side effects.

A previous study examined the effective factors in prostate recovery after the discontinuation of 5ARI [7]. As an extension, this study examined the patients' clinical course after intermittent 5ARI use.

MATERIALS AND METHODS

1. Study Population

This study was performed retrospectively on BPH patients who visited a doctor's outpatient department between March 2009 and May 2017. After measuring the prostate volumes by transrectal ultrasonography (TRUS), patients with a prostate volume larger than 30 ml were selected as subjects. Patients who underwent BPH-related surgery, such as transurethral resection of the prostate or diagnosed with prostate cancer by a prostate biopsy in the study period, were excluded. The Institutional Review Board of National Police Hospital (no. 11100176-201810-HR-006) approved this study and exempted it from written informed consent.

2. Study Design

Fig. 1 shows the course of the study and patient selection. The patients began to take 5ARI (finasteride or dutasteride) after the serum prostate specific antigen (PSA) level was measured. After six months of 5ARI medication, the size of the prostate was re-measured. Patients whose prostate volume was reduced to less than 10% of the original volume were excluded, and the remaining patients stopped taking 5ARI. After at least one year of discontinuance, a third measurement of the prostate size was performed, and the recovered volume was calculated. 5-ARI medication was restarted when the prostate volume recovered to more than 50% of its reduced size. After 1-year medication, the final prostate measurement was taken. An international prostate symptom score (IPSS) questionnaire and uroflowmetry were conducted every time TRUS had been performed, and the IPSS scores and maximum flow rate (Qmax) were collected

3. Statistical Analysis

After collecting the data, the differences in prostate size, reduced size and rate, PSA scores, IPSS scores, and Qmax between after the first and second medication were analyzed statistically using a paired t-test. SPSS for Windows ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and two-sided $p<0.05$ were considered significant.

RESULTS

Among the patients, 60 patients with a mean age of 65.1 years were included in the study. Table 1 lists the changes in prostate volume, serum PSA levels, IPSS scores, and Qmax measured by uroflowmetry. The mean prostate size, IPSS scores, and Qmax showed improvement after each medication and aggravation after discontinuation. On the other hand, the serum PSA levels showed a different pattern: a decrease from 0.87 ng/ml at the first medication to 0.57 ng/ml, but increased from 1.1 ng/ml at the second medication to 1.37 ng/ml.

The results of the first and second medications were compared statistically and are summarized in Table 2. The mean prostate size increased significantly from 23.5 ml after the first medication to 27.2 ml after the second. The absolute value (8.8 ml→7.7 ml) and ratio (27%→21%) of the reduced size compared to the size before medication decreased significantly after the second medication compared to that after the first medication. Qmax (24.5 ml/s→20.6 ml/s) also showed a significant decrease after the second medication compared to that after the first. On the other hand, there were no statistically significant differences in the IPSS scores in both the total and quality of life scores.

DISCUSSION

During intermittent medication of 5ARI, although both medications show improvements in the prostate volume, Qmax, and IPSS scores, the second medication was less effective in reducing the prostate size and serum PSA level compared to the first medication, which resulted in limited improvement of Qmax by uroflowmetry. On the other hand, there were no significant differences between the symptoms

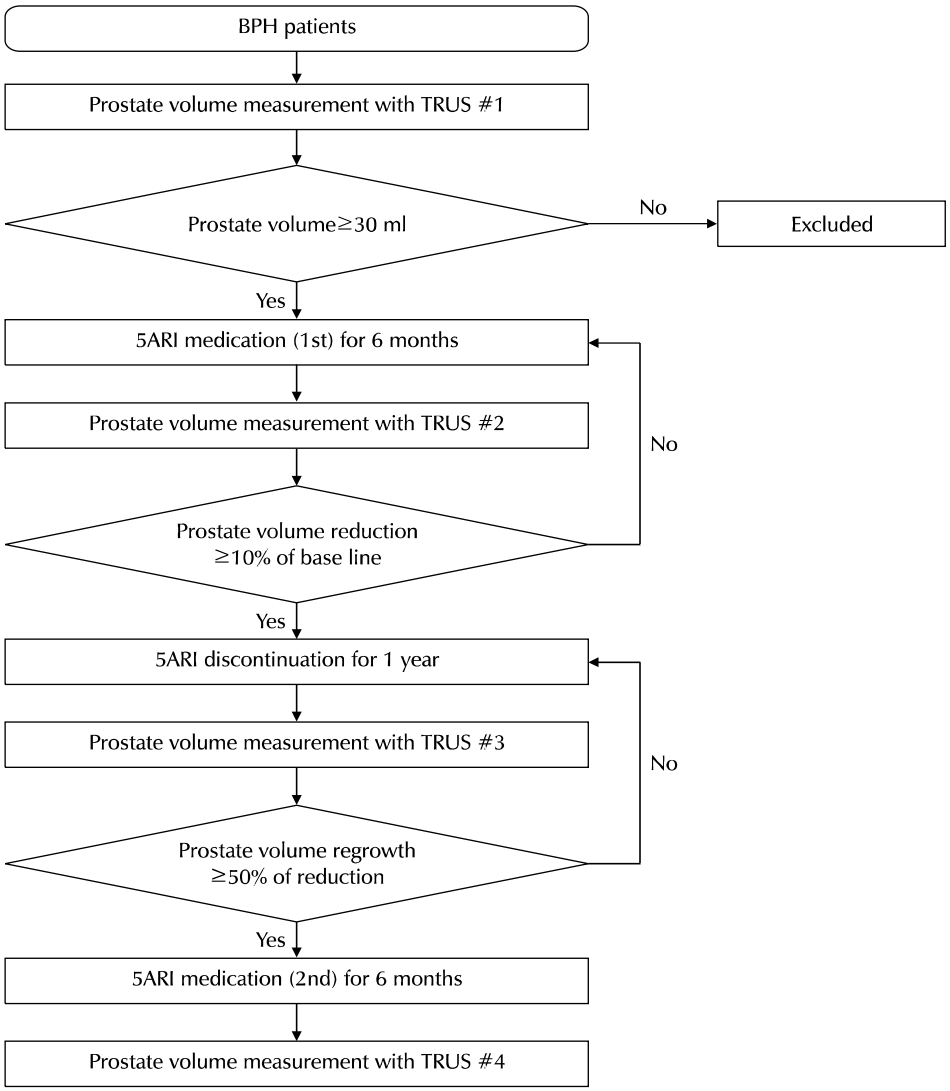

Fig. 1. Flow chart of the study course and patient selection. BPH: benign prostate hyperplasia, TRUS: transrectal ultrasonography, 5ARI: 5-alpha reductase inhibitors.

Table 1. Changes in the clinical features during the 1st medication, discontinuation, and 2nd medication (n=60)

Parameters	Initial	After 1st medication	After discontinuation	After 2nd medication
Prostate volume (ml)	32.3±4.0	23.5±3.3	34.9±5.8	27.2±6.3
Serum PSA (ng/ml)	0.87±0.57	0.57±0.42	1.1±0.7	1.37±2.7
IPSS scores				
Total	11.4±4.4	9.7±5.9	10.4±5.7	9.6±6.0
QOL	3.1±1.3	2.5±1.2	3.6±1.3	2.4±1.6
Qmax (ml/s)	18.2±8.2	24.5±8.6	17.6±5.4	20.6±5.9

Values are presented as mean±standard deviation.
PSA: prostate specific antigen, IPSS: international prostate symptom score, QOL: quality of life, Qmax: maximum flow rate.

felt by the patients measured by IPSS after the 1st and 2nd medication. This suggests that the score reflects the patients' satisfaction from the improvement of symptoms after medication, rather than the patient's actual symptoms, but the precise reason may be determined by further long-term research.

BPH is one of the most common diseases in men aged over 50 years, and its prevalence increases with age [8]. Although not life threatening, LUTS caused by BPH, such as hesistancy, poor or intermittent stream, and nocturia, may deteriorate the quality of life. The progressive nature of BPH can be quantified by increases in the LUTS severity according to the IPSS, Qmax, episodes of acute urinary retention, or the need for BPH-related surgery [9]. Two types

Table 2. Results of statistical analysis between 1st and 2nd medication

Parameters	After 1st medication	After 2nd medication	p-value
Prostate volume (ml)	23.5±3.3	27.2±6.3	<0.001
Prostate volume reduction			
Size (ml)	8.8±4.1	7.7±7.3	0.027
Ratio (%)	27±0.1	21±0.19	<0.001
Serum PSA	0.58±0.42	1.37±2.7	<0.001
IPSS scores			
Total	9.7±5.9	9.6±6.0	0.473
QOL	2.5±1.2	2.4±1.6	0.388
Qmax (ml/s)	24.5±8.6	20.6±5.9	<0.001

Values are presented as mean±standard deviation.
PSA: prostate specific antigen, IPSS: international prostate symptom score, QOL: quality of life, Qmax: maximum flow rate.

of treatments are available for patients with BPH: medical treatment and surgical treatment [10]. α-blockers, one of first-line medical treatments in BPH, bind to the alpha-1 receptors and relax the smooth-muscle tone in the prostate and bladder neck [11]. α-blockers relieve urinary symptoms rapidly and improve the IPSS score and Qmax with few adverse effects [12]. On the other hand, α-blockers do not block the progression of prostate enlargement and cannot affect the long-term risk of acute urinary retention or BPH-related surgery [13].

The other first-line medical treatment is 5ARI. 5ARI blocks the action of 5-alpha reductase, which converts sex-steroid hormone testosterone to dihydrotestosterone, leading to a decrease in the enlarged prostate volume and alleviation of LUTS by BPH. When used as a monotherapy, the speed of symptom control is relatively slower than α-blockers. When used in the long term, however, 5-ARI also helps reduce the risk of acute urinary retention and BPH-related surgery [14]. Madersbacher et al. [15] reported that after long-term use of 5ARI, the serum PSA level and prostate volume decreased by approximately 50% and 20%, respectively. In the present study, after the first medication, the serum PSA level and prostate volume decreased by 33% and 27%, respectively.

Despite the effects of 5ARI, the range of side effects makes long-term use difficult. Sexual dysfunction, one of the most common side effects, appears in the form of decreased libido, erectile dysfunction, and ejaculation disorder, which especially affects the compliance of relatively younger patients [16,17]. In addition, cosmetic changes, such as gynecomastia, and psychiatric side effects, such as anxiety and mood disorders, have been reported [18,19]. Because of this, some urologists consider discontinuing 5ARI if the size of the prostate is reduced sufficiently, but the duration of the appropriate treatment is not yet determined.

After discontinuing 5ARI, the prostate size recovered rapidly to its premedication size. Stoner [20] and Kim et al. [6] reported that the prostate regrew to more than 95% of the baseline after stopping 5ARI for 12 weeks and one year, respectively. In a previous study [7], the mean prostate volume was reduced 28% during 5ARI medication but regrew to 97.1% of the baseline after one year of discontinuation. In this study, the regrowth rate of the prostate reached 108% after one year of discontinuation. The precise mechanism of this rapid regrowth is unclear, but there are several hypotheses. The hyperplastic changes in BPH are an androgen-dependent process, and it is possible that the sensitivity to DHT is increased or overly activated because of the prolonged pharmacological inhibition of 5-alpha reductase [21]. Another possible hypothesis is related to the androgen receptors, which become more sensitive or up-regulated during treatment with 5ARI, and may be considered as an alternative mechanism [21].

Given that this study is a fragmentary study conducted at a single institution, it had several limitations. First, this study investigated the clinical course of patients who used 5-ARI intermittently. On the other hand, to determine the true significance of intermittent use of the drug, it will be necessary to compare it with patients who continue to use the drug as a control group. Unfortunately, this study could not include those patients owing to a lack of time. Second, two types of 5ARI, finasteride and dutasteride, may have had different effects on the patient's clinical course. The draft of the plan was to separate the two medication groups and compare them statistically. In some cases, however, the two-drugs were used interchangeably, which made it difficult to divide the groups. Because of this, this categorization in this study was excluded. Third, taking α-blockers can affect IPSS or uroflowmetry results. Therefore, it is more accurate to unify the use or type of drug in all patients. In that case, however, the number of subjects collected from one institution was so small that the study did not consider whether to take α-blockers. Further studies will overcome these limitations.

The strength of this study is that the effects experienced by patients on re-use after discontinuing 5ARI could be observed. Several studies have investigated the clinical

course of patients, such as prostate regrowth, worsening LUTS, and increasing serum PSA levels, when they stop taking 5ARI, but no study has investigated the clinical course after re-use of 5ARI.

CONCLUSIONS

The results showed that after discontinuation, the effects of 5ARI on reducing the prostate size and improving Qmax decreased. On the other hand, there was no difference in the urinary symptoms between the first and second medications. If this is prolonged, it may also influence the effects of 5ARI on decreasing the prevalence of urine retention or BPH-related surgery. Nevertheless, longer-term studies will be needed to demonstrate this. If urologists plan to discontinue 5ARI in BPH patients, they should consider that the drug effects might have a limitation in future re-use, and should consider re-dosing 5ARI before the prostate volume becomes too large. Further studies will help improve the urinary symptoms and minimize the side effects of 5ARI in BPH patients.

CONFLICT OF INTEREST

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

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AUTHOR CONTRIBUTIONS

K.C. participated in data collection, performed the statistical analysis and wrote the manuscript. B.K. participated in data collection. I.C.C. participated in the the study design and helped to draft the manuscript. S.K.M. participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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