



Patient's Factors Correlated with Prostate Volume Recovery after 5 Alpha Reductase Inhibitor Discontinuation

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Purpose: The 5 alpha reductase inhibitor (5ARI) reduces the size of the prostate and alleviates lower urinary tract symptoms. After stopping 5ARI, the prostate quickly recovers to its pre-medication size. The purpose of this study was to investigate the factors affecting the restoration of prostate size after 5ARI discontinuation.

Materials and Methods: Between March 2009 and May 2017, patients who visited an outpatient clinic and were diagnosed with benign prostatic hyperplasia were selected and start 5ARI medication. After 6 months of medication, the patients stopped medication for 1 year. Meanwhile, we measured the prostate volumes of patients 3 times (before and after medication, after discontinuation) and divide the patients into 3 groups (maintained, intermediate, and restored) with recovered prostate volume ratio. After classification, we investigated the relationship between the variable factors (age, serum prostate-specific antigen, initial volume, reduced volume after medication) between groups.

Results: Among the 147 selected patients, the mean age and plasma PSA level were 61.6 ± 7.9 and 0.8 ± 0.6 , respectively. The mean initial prostate volume was 32.3 ± 4.2 ml, which reduced to 23.2 ± 3.2 ml after medication. After one year of discontinuation, the mean volume was 31.4 ± 6.4 ml, with restoration to 101.5% of the reduced size. We noticed a tendency that patients with faster prostate volume recovery were generally older than those with slower recovery; however, this was not statistically significant. Other factors showed no relationship with prostate recovery.

Conclusions: When using 5ARI in elderly patients, continuous treatment seems better than intermittent treatment. If discontinuation is needed, short term follow-up is recommended.

Keywords: Benign prostate hyperplasia; 5 alpha reductase inhibitor

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive disease that causes lower urinary tract symptoms (LUTS) in aged men [1]. The 5 alpha reductase inhibitor (5ARI)

is widely used as the first-line treatment of BPH with alpha-adrenergic receptor antagonists (α -blockers). α -Blockers, such as terazosin, tamsulosin, doxazosin, or alfuzosin, relax the smooth-muscle tone in the prostate and bladder neck [2], while 5ARIs, such as finasteride or dutasteride, directly reduce

the size of the enlarged prostate and alleviate LUTS [3].

However, 5ARI has been shown to cause side effects, such as sexual dysfunction and anxiety, which can adversely affect patients' compliance and continuous treatment [4]. For this reason, some physicians may temporarily stop medication if the prostate volume is sufficiently reduced. After stopping 5ARI, the prostate quickly recovers to its pre-medication size, with individual differences [5]. However, to the best of our knowledge, there are only a few studies evaluating the factors that determine the rate of restoration of prostate volume. Hence, the purpose of this study was to investigate the factors affecting the restoration rate of prostate volume after the discontinuation of 5ARI.

MATERIALS AND METHODS

1. Study Population

Between March 2009 and May 2017, patients who visited an outpatient clinic, were diagnosed with BPH, and underwent transrectal ultrasonography (TRUS) were included for analysis. After measurement, patients with a prostate volume larger than 30 ml were selected. Patients who underwent BPH surgery, such as transurethral resection of prostate or diagnosed with prostate cancer by prostate biopsy in study period were excluded. Our study is approved by the institutional review board of National Police Hospital (No. 11100176-201810-HR-006) and the requirement for written informed consent was waived.

2. Study Design

The selected patients began to take 5ARI after measuring the serum prostate-specific antigen (PSA) level. After a 6-month medication period, the size of the prostate was re-measured. Patients whose prostate volume was reduced 10% or less of the original volume were excluded, and the rest stopped medication. After one year of discontinuation, we performed a 3rd measurement of the prostate size, and calculated the recovered volume. The patients were then classified into 3 groups (maintained, intermediate, and restored) according to the ratio of recovered volume after discontinuation to reduced volume after medication. The maintained group included patients whose prostate volume was recovered by less than 20% of the reduced size. The intermediate group included those who recovered between 20% and 80% and the restored

group included those who recovered by more than 80% of reduced size.

3. Statistical Analysis

After classification, we statistically analyzed the relationship of patients' age, serum PSA level, prostate size of pre-medication, and reduced ratio after medication among the 3 groups using t-test. IBM SPSS Statistics windows ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses; two-sided $p < 0.05$ were considered statistically significant.

RESULTS

1. General Characteristics

Among the total patients, 147 patients were included in this study. The mean age and plasma PSA level were 61.6 ± 7.9 and 0.8 ± 0.6 , respectively. The mean prostate volume before 5ARI medication was 32.3 ± 4.2 ml, which was reduced to 23.2 ± 3.2 ml after medication, with a shrinkage of $27.5 \pm 0.1\%$. After one year of discontinuation, the mean prostate volume was 31.4 ± 6.4 ml, with restoration 101.5% of reduced size. Patients were divided according to the degree of prostate size recovery; 16 patients in the maintained group (10.9%), 48 in the intermediate group (32.6%), and 83 in the restored group (56.5%). Table 1 shows the patient characterization of each group.

2. Relationships of Prostate Volume Recovery and Clinical Factors

Fig. 1. shows the box plot of each patients' factors and results of t-tests in the 3 groups. We found a weak tendency that older patients had faster prostate volume recovery than younger patients who showed slower recovery; however, this was not statistically significant between the groups. Otherwise, the prostate volume before medication, reduced volume ratio after 5ARI medication, and serum PSA all showed no correlation with recovered prostate volume. There were some t-tests with p-value of less than 0.05; however, the change of the mean value was not consistent; the results showed no correlation with prostate recovery.

DISCUSSION

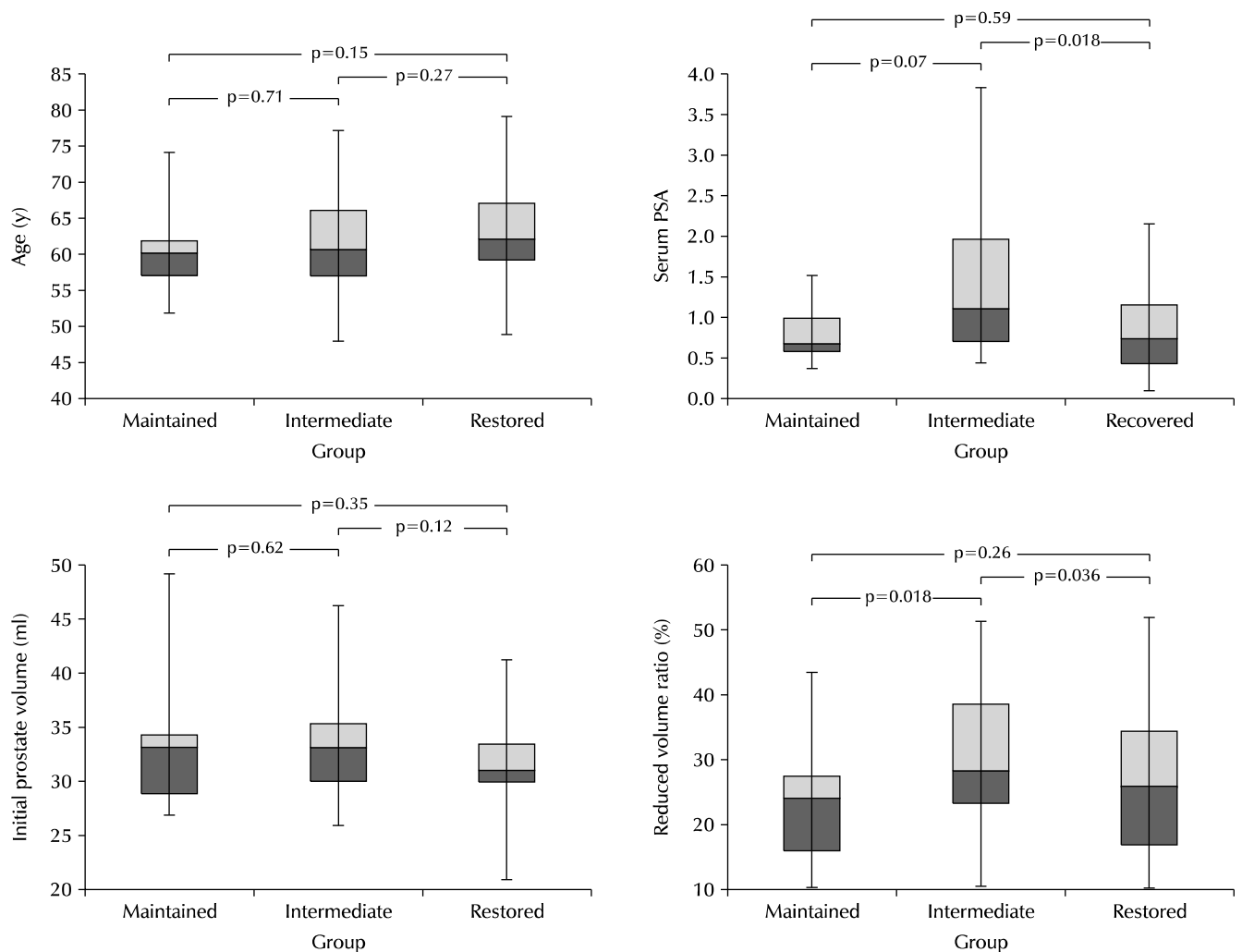
BPH is a progressive disease commonly associated with

Table 1. General characteristics of each patients groups

Characteristic	Maintained group (n=16)	Intermediate group (n=48)	Restored group (n=83)	Total (n=147)	p-value		
					Maintained-Intermediate	Maintained-Restored	Intermediate-Restored
Age (y)	60.0±5.0	60.8±10.7	62.4±6.2	61.6±7.9	0.71	0.15	0.27
Serum PSA	0.9±0.4	1.2±0.8	0.8±0.5	0.8±0.6	0.07	0.59	0.018
Initial prostate volume (ml)	32.9±5.5	33.6±4.4	31.5±3.4	32.3±4.2	0.62	0.35	0.12
Prostate volume after 5-ARI medication (ml)	24.8±2.9	23.1±3.5	22.9±3.0	23.2±3.2			
Reduced ratio after 5-ARI medication (%)	23.1±0.1	30.6±0.1	26.5±0.1	27.5±0.1	0.018	0.26	0.036
Prostate volume after 5-ARI discontinuation (ml)	23.5±3.3	28.3±4.4	34.7±5.6	31.4±6.4			

Values are presented mean±standard deviation.

PSA: prostate-specific antigen, ARI: alpha reductase inhibitor.

**Fig. 1.** Box plot for variable factors distribution in each groups and the results of t-tests. PSA: prostate-specific antigen.

LUTS in aged men, resulting in complications, such as acute urinary retention, recurrent urinary tract infection, hematuria, urinary bladder stones, and renal insufficiency [6]. The first lines of treatment for BPH are α -blocker and

5ARI. α -Blockers relax the smooth-muscle tone in the prostate and bladder neck, alleviating LUTS [2]. They show rapid improvement of the maximum flow rate (Q_{max}) and quality of life with little adverse effects, but have no effect

in the prostate growth [7]. For this reason, a single medication of α -Blockers can delay complication of BPH, but may be limited to a reduced prevalence in the long term [8].

The 5-alpha reductases (5-AR) are a family of enzymes, widely distributed in many tissues, including the central nervous system (CNS) [9], and responsible for converting testosterone to dihydrotestosterone (DHT), which is important for the progression of BPH [10]. The 5ARI medication inhibits 5-AR and blocks the formation of DHT, halt or reverse the growth of BPH, and alleviate the symptoms of BPH [3]. A previous study reported that the serum PSA level and prostate volume were decreased by approximately 50% and 20%, respectively, after the treatment with 5ARI [11]. In another study, men taking 5ARI have a 57% reduction in the risk of acute urinary retention compared with those taking placebo and a 34% reduction in the risk of surgery [12].

However, substantial number of patients taking 5ARI experience side effects. In sexual function, studies of Nickel et al. [13] and Tenover et al. [14] showed that the prevalence of erectile dysfunction and ejaculation disorder were higher in the finasteride group than in the placebo group. Hudson et al. [15] reported that the loss of libido is also increased after a 12-month treatment of 5 mg finasteride. In the CNS, since 5-AR also has a role in conversion of precursors into various neurosteroids, such as androstanediol, allopregnanolone, tetrahydrocortisol, tetrahydrocorticosterone, and tetrahydrodeoxycorticosterone [9], 5ARI medication can reduce neuroactive steroids in CNS and plasma [16]. In particular, a reduction in the level of allopregnanolone, which plays a role in the protection against ischemia, maintenance of blood brain barrier integrity, and in memory and learning, may cause anxiety and depressive symptoms [16]. These adverse effects can lower the patient compliance and continuity of treatment [17].

After discontinuation of 5ARI, the prostate will quickly return to its pre-medication size. Stoner [18] demonstrated that the prostate volume returned to near the baseline values at 12 weeks after discontinuation of 5ARI. In a study by Kim et al. [5], the mean percentage of the prostate regrowth had reached 95.5% of the baseline prostate volume one year after discontinuation of dutasteride. The reason for this rapid recovery of size after stopping the 5ARI medication remains unclear; however, there are several possible 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 as a result of the prolonged pharmacologic inhibition of 5AR by the 5ARI [19]. Another hypothesis has to do with Androgen receptors, which become more sensitive or up-regulated during treatment with 5ARI and may be considered as an alternative mechanism [19].

Although we failed to confirm the statistical significance, the main strength of our study is that we explored the factors involved in the recovery of the prostate size when 5ARI was discontinued. There are a number of clinical trials after discontinuation of 5ARI. Kim et al. [5] demonstrated that the withdrawal of 5ARI during a combination therapy resulted in prostate regrowth, deterioration of LUTS, and increased level of PSA. Liaw et al. [20] showed that the therapeutic effects were maintained without progression of BPH in 64.3% and 62.5% of patients one year after the discontinuation of tamsulosin and finasteride following combination therapy, respectively. However, there were no studies that investigated the factors associated with prostate recovery. Another strength is regular patient's follow up with 6 months of medication and one year of discontinuation. This minimizes the possible bias caused by time difference.

Given that this study is a fragmentary study conducted by a single institution, it has several limitations. First, the number of included patients was small and it took place in only one institution. This may have been the source of lack of statistical significance. Second, we did not consider the difference between the two 5ARI substances—finasteride vs. dutasteride. Because several patients changed drugs due to the lack of efficacy or side effects, it was difficult to statistically analyze this component. Third, it was difficult to verify the patients' past compliance in present time. Fourth, we excluded patients who underwent BPH-related surgery or were diagnosed with prostate cancer due to difficulty in prostate volume measurement and difference in follow up term, and this may have caused selection bias.

CONCLUSIONS

In this study, we found a weak positive correlation between patient's age and recovering speed of prostate volume after 5ARI discontinuation, without statistical significance. Other factors, such as PSA, prostate volume

before medication, and reduced size after medication, showed to have no association with. When using 5ARI in elderly patients, it seems better to use the medication continuously rather than intermittently; and if discontinuation is needed, short term follow-up is recommended.

CONFLICT OF INTEREST

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

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