KJU
Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2011.52.10.681

Voiding Dysfunction

Effect of Shifting from Combination Therapy to Monotherapy of α-Blockers or 5α-Reductase Inhibitors on Prostate Volume and Symptoms in Patients with Benign Prostatic Hyperplasia

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Purpose: Combination therapy of α-blockers and 5α-reductase inhibitors (5-ARIs) is widely used for the treatment of benign prostatic hyperplasia (BPH). We aimed to study the effect on prostate volume and symptoms of shifting to monotherapy in patients who previously received a combination therapy.

Materials and Methods: A prospective study was conducted of 60 patients who were diagnosed with BPH. Patients were aged 45 years or older and had a prostate volume of 30 cc or more, International Prostate Symptom Score (IPSS) of 12 or above, maximal flow rate (Qmax) of 15 ml/s or less, and prostate-specific antigen (PSA) level of less than 10 ng/ml. The patients initially received a combination therapy of doxazosin 4 mg/day and finasteride 5 mg/day for 3 months and were then randomly assigned to receive monotherapy for 3 months. The factors were then compared.

Results: A total of 30 patients were assigned to doxazosin (group 1) and 30 to finasteride (group 2) after the combination therapy. The percentage changes in prostate volume, IPSS, and Qmax during the period from post-combination therapy to post-monotherapy were not significantly different between the two groups (p=0.052, 0.908, 0.081), whereas PSA significantly decreased in group 2 ($p < 0.001$). IPSS was not significantly different at post-combination therapy and at post-monotherapy in both groups (p=0.858, 0.071). The prostate volume significantly increased from 40.97 cc at post-combination therapy to 44.29 cc at post-monotherapy in group 1 (p=0.001) and insignificantly increased from 38.32 cc to 38.61 cc in group 2 (p=0.696).

Conclusions: Although the duration of drug administration was short in this study, 5-ARI monotherapy could maintain the alleviated symptoms and reduce the risk of acute urinary retention and surgery due to prostate regrowth in BPH patients whose symptoms improved with combination therapy.

Key Words: *Adrenergic alpha-antagonists; 5-alpha-reductase inhibitors; Combination; Drug therapy; Prostatic hyperplasia*

Article History:
received 15 April, 2011
accepted 12 August, 2011

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common disease process that affects an increasing percentage of men as they age. It is prevalent in the 40- to 79-year-old age group, with incidences ranging from 14% to 56% in different countries [1]. BPH-induced lower urinary tract symptoms (LUTS) are bothersome to most patients and substantially impact their quality of life. In addition, BPH can be a progressive disease and may lead to acute urinary retention (AUR) and BPH-related surgery [2]. The main goals of therapy for BPH are to improve LUTS and enhance quality of

life. Other goals include slowing disease progression, preventing complications (e.g., AUR), and delaying the need for surgery [3,4]. Until recently, the most widely recognized standard treatment for BPH was transurethral resection of the prostate (TURP). Since Caine et al first reported on the possibility of drug therapy, however, many effective drugs have been developed, and in recent years, drug therapy has been used as a mainstream modality in most patients [5,6]. Alpha-adrenergic receptor blockers (α-blockers) and 5α-reductase inhibitors (5-ARIs) have been mainly used for the medical treatment of BPH. α-blockers (e.g., doxazosin, terazosin, tamsulosin) decrease smooth muscle tone in the prostate gland, prostatic capsule, prostatic urethra, and bladder [7]. In contrast, 5-ARIs (e.g., finasteride, dutasteride) reduce the prostate volume by inhibiting the production of dehydrotestosterone, which is the primary androgen driving both normal prostate development and the hyperplasia of the prostatic transitional zone that is responsible for the development of BPH [8]. The Medical Therapy of Prostatic Symptoms Study (MTOPS) reported that the risk of AUR in patients with BPH decreased considerably with finasteride monotherapy or with the combination of doxazosin and finasteride compared with doxazosin monotherapy. The study added that α-blocker monotherapy could only delay the onset of complications, such as AUR, whereas combination therapy of α-blockers and 5-ARIs could reduce the risk of AUR and surgical treatment [9]. Since Glassmann et al first suggested that combination therapy of terazosin and finasteride could enhance the treatment effect for BPH by observing that, compared with terazosin monotherapy, the combination therapy significantly increased the apoptotic index of prostatic cells, this combination therapy has been widely used [10].

In South Korea, many studies have reported on the risk factors of AUR and prostatic surgery and the degree of improvement in LUTS and maximal flow rate (Qmax) in patients with BPH who receive combination therapy of α-blockers and 5-ARIs. However, the effect on the prostate of shifting from combination therapy to monotherapy of α-blockers or 5-ARIs in patients with BPH is not known. BPH is common among older males, and most of these patients have underlying comorbidities such as hypertension and diabetes. Thus, these patients feel burdened by the number of drugs they have to take. By applying monotherapy after combination therapy, the cost and inconvenience of a second medication, as well as the side effects of combination therapy, could be reduced. Therefore, we conducted a prospective, randomized, and comparative single-center trial to investigate the effect on the prostate volume and symptoms of shifting from combination therapy of α-blockers and 5-ARIs to monotherapy of either α-blockers or 5-ARIs.

MATERIALS AND METHODS

A prospective study was conducted on 60 patients who were diagnosed with BPH from February 2010 to February 2011 at the Department of Urology, Sahmyook Medical Center. Patients were aged 45 years or older and had a prostate volume of 30 cc or more based on transrectal ultrasonography (TRUS), an International Prostate Symptom Score (IPSS) of 12 or above, Qmax of 15 ml/s or less, and prostate-specific antigen (PSA) level of less than 10 ng/ml. Patients who had a PSA level of 4-10 ng/ml underwent TRUS-guided prostate needle biopsy (10- or 12-core), and patients who were diagnosed with BPH were included in the study. Patients who had a history of TURP, had prostatitis or recurrent urinary tract infection, had a PSA level of 10 ng/ml or more, or were taking α-blockers or other drugs such as 5-ARIs that are known to exert an influence on the PSA level were excluded from the study.

The subjects had their prostate volume, PSA, IPSS, and Qmax measured at the time of their presentation to the hospital. The prostate volume was calculated by measuring the height, width, and length by using TRUS and by putting these values into the ellipsoid formula of 3.14/6x (height)x(width)x(length). TRUS was performed by one urologist who was blinded to patient assignment. PSA was measured by enzyme immunoassay, and it was measured before the TRUS to minimize interference. Uroflowmetry was performed with the patient in a standing position, and the voided volume and Qmax were recorded continuously during micturition with a minimum voided volume $\geq$125 ml.

The subjects received combination therapy of doxazosin 4 mg/day and finasteride 5 mg/day as an initial drug treatment for 3 months and then underwent measurements of prostate volume, PSA, IPSS, and Qmax. After the 3-month combination therapy, the subjects were randomly assigned to receive monotherapy of either doxazosin (group 1) or finasteride (group 2) for 3 months. The prostate volume, PSA, IPSS, and Qmax were then measured. All patients received a combination of 2 tablets (doxazosin with finasteride) for 3 months, followed by 3 months of monotherapy of 1 tablet (doxazosin or finasteride) without use of a placebo. All patients were blinded to drug assignment.

The percentage changes in each factor during the period from post-combination therapy to post-monotherapy of each group were compared and analyzed. The values of each factor measured at post-monotherapy were subtracted from the values of each factor measured at post-combination therapy. The remainder was divided by the values measured at post-combination therapy and was used as the percentage of change.

For statistical analysis, a Student's t-test was performed by using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at a p-value $<$ 0.05.

RESULTS

The mean age among the 60 subjects was 68.2 years. Before the treatment, the mean prostate volume was 48.6 cc; mean PSA, 1.88 ng/ml; mean IPSS, 16.87; and mean Qmax, 11.53 ml/s. Of the entire 60 subjects, 30 (group 1) received dox-

azosin monotherapy and 30 (group 2) received finasteride monotherapy after the combination therapy of doxazosin 4 mg/day and finasteride 5 mg/day. Age (67.57 vs 68.83 years, p=0.533), prostate volume (50.27 vs 46.89 cc, p=0.453), PSA (2.03 vs 1.72 ng/ml, p=0.484), IPSS (16.70 vs 17.03, p=0.822), and Qmax (11.58 vs 11.48 ml/s, p=0.879) measured before combination therapy were not significantly different between the two groups (Table 1).

For group 1, after 3 months of combination therapy, the mean prostate volume significantly decreased from 50.27 cc to 40.97 cc, mean IPSS from 16.7 to 11.43, and mean PSA from 2.03 ng/ml to 1.09 ng/ml, whereas mean Qmax significantly increased from 11.58 ml/s to 15.01 ml/s ($p<0.001$, respectively). For group 2, after 3 months of combination therapy, the mean prostate volume significantly decreased from 46.89 cc to 38.22 cc, mean IPSS from 17.03 to 13.10, and mean PSA from 1.72 ng/ml to 1.23 ng/ml ($p<0.001$, $p<0.001$, p=0.015, respectively), whereas mean Qmax significantly increased from 11.47 ml/s to 16.88 ml/s ($p<0.001$). The percentage change in each factor after 3 months of combination therapy was not significantly different between the two groups: prostate volume (−15.89 vs −18.26%, p=0.451), IPSS (−29.88 vs −25.03%, p=0.387), Qmax (33.78 vs 59.54%, p=0.081), and PSA (−36.48 vs −23.35%, p=0.172) (Table 2).

After 3 months of monotherapy of either doxazosin or finasteride administered after 3 months of combination therapy, for group 1, the mean prostate volume significantly increased from 40.97 cc to 44.29 cc; mean PSA increased from 1.09 ng/ml to 1.63 ng/ml ($p<0.001$ and $p<0.001$, respectively); mean IPSS increased from 11.43 to 11.57 (p=0.858); and Qmax decreased from 15.01 ml/s to 14.15 ml/s, although not significantly (p=0.131). For group 2, the mean prostate volume increased from 38.32 cc to 38.61 cc and mean IPSS increased from 13.1 to 14.00; mean PSA decreased from 1.23 ng/ml to 0.87 ng/ml, although not significantly (p=0.696, p=0.071, and p=0.051, respectively). The mean Qmax significantly decreased from 16.88 ml/s to 14.66 ml/s (p=0.014). The percentage change in prostate volume (+7.69% vs. +1.98%, p=0.052), IPSS (+13.03% vs. +11.94%, p=0.908), and Qmax (−3.55% vs. −12.08%, p= 0.081) during the period from post-combination therapy to post-monotherapy of either doxazosin or finasteride was not significantly different between the two groups, whereas PSA significantly decreased in group 2 (+86.04% vs. −36.35%, $p<0.001$)(Table 2).

After 6 months of treatment (combination therapy for 3 months and monotherapy for 3 months), the prostate volume was 91.51% of the baseline volume in group 1 and 83.12% in group 2. The rates were significantly different

Table 1. Patient baseline characteristics in group 1 and group 2

	Total	Group 1	Group 2	p-value
No. of patients	60	30	30	
Age (yr)	68.20±8.18	67.57±8.50	68.83±7.95	0.553
Prostate volume (cc)	48.58±17.23	50.27±20.23	46.89±13.75	0.453
PSA (ng/ml)	1.88±1.68	2.03±1.80	1.72±1.57	0.484
IPSS	16.87±5.66	16.70±4.78	17.03±6.50	0.822
Qmax (ml/s)	11.53±2.60	11.58±2.15	11.48±3.02	0.879

PSA: prostate-specific antigen, IPSS: International Prostate Symptom Score, Qmax: maximal flow rate

Table 2. Comparison of changes in prostate volume, PSA, IPSS, and Qmax according to study duration between the two groups

		Prostate volume (cc)			PSA (ng/ml)		
		Group 1	Group 2	p-value	Group 1	Group 2	p-value
Duration (wk)	0	50.27±20.23	46.89±13.75	0.453	2.03±1.80	1.72±1.57	0.484
	12	40.97±14.03	38.32±12.43	0.442	1.09±0.82	1.23±1.37	0.631
	24	44.29±16.73	38.61±11.00	0.126	1.63±1.18	0.87±0.78	0.004
Change from 0 to 12 (%)		−15.89±14.01	−18.26±9.81	0.451	−36.48±38.39	−23.35±34.99	0.172
Change from 12 to 24 (%)		7.69±12.31	1.98±9.84	0.052	86.04±81.67	−36.35±146.40	<0.001
		IPSS			Qmax (ml/s)		
		Group 1	Group 2	p-value	Group 1	Group 2	p-value
Duration (wk)	0	16.70±4.78	17.03±6.50	0.822	11.58±2.15	11.47±3.02	0.879
	12	11.43±4.95	13.10±6.46	0.267	15.01±3.32	16.88±6.01	0.143
	24	11.57±3.96	14.00±6.28	0.079	14.15±4.21	14.66±6.34	0.715
Change from 0 to 12 (%)		−29.88±26.09	−25.03±15.73	0.387	33.78±34.65	59.54±71.03	0.081
Change from 12 to 24 (%)		13.03±46.21	11.94±22.82	0.908	−3.55±25.62	−12.08±25.37	0.200

PSA: prostate-specific antigen, IPSS: International Prostate Symptom Score, Qmax: maximal flow rate

between the two groups (p=0.029)(Table 2).

Among the 60 subjects, AUR or prostatic surgery did not occur during the 6 months of treatment.

DISCUSSION

BPH is a long-term, progressive disease that considerably impacts the quality of life of patients by causing LUTS. As the disorder advances, it can lead to a worsening of symptoms and an increased risk of serious outcomes, such as AUR and disease-related surgery [11]. Recently, the attention related to drug treatment for BPH has focused on reducing LUTS as well as preventing the progression of BPH by reducing AUR or risk of surgery related to BPH. Because combination therapy of α-blockers and 5-ARIs is more effective than either drug alone in reducing the risk of BPH progression and improving symptoms, this combination therapy is commonly used for the treatment of BPH. With combination therapy, the α-blocker relieves symptoms until the 5-ARIs have time to resolve the obstruction and improve the symptoms. Once the prostate volume is decreased and the LUTS are improved by the combination therapy, monotherapy might be possible with either an α-blocker or a 5-ARI.

Gormley et al reported that significant reductions in prostate volume occurred within 3 months of therapy with finasteride [12]. In the present study, after 3 months of combination therapy, the patients received 3 months of monotherapy. After combination therapy for 3 months, we observed that prostate volume decreased by 15.89% and by 18.26% in groups 1 and 2, respectively (Table 2).

Stoner reported that the prostate volume returned to near baseline values at 12 weeks after the finasteride was discontinued [8]. Jeong et al suggested that as the prostate regrows, after discontinuing the 5-ARIs, the LUTS significantly worsened compared with the values after 1 year of combination therapy despite maintenance with the α-blocker [13]. The results of that study showed that prostate shrinkage in the dutasteride-treated group was 73.9% of the baseline level and was 75.5% in the finasteride-treated group at 12 months after combination therapy. At 1 year after the 5-ARIs had been withdrawn, the mean percentage of prostate regrowth was 20.7% and 18.6% in the finasteride-treated group and the dutasteride-treated group, respectively. Thus, the prostate volume in the finasteride-treated group had increased to ≤ 91.1% of the baseline value at 1 year after cessation of the drug. The prostate regrowth in the dutasteride-treated group had reached ≤87.6% of the baseline volume [13].

In the present study, after 3 months of combination therapy, the prostate volume was 84.1% of the baseline volume in group 1 and 81.7% in group 2. In group 1, in which only doxazosin was administered and finasteride was discontinued after 3 months of combination therapy, the mean prostate volume significantly increased by 7.69% from 40.97 cc to 44.29 cc, indicating prostate regrowth ($p < 0.001$). In group 2, in which only finasteride was administered and doxazosin was discontinued after 3 months of combination therapy, the mean prostate volume increased, although not significantly, by 1.98% from 38.32 cc to 38.61 cc without considerable regrowth (p=0.696). After combination therapy and monotherapy for 6 months, the percentage change in prostate volume was significantly different between the two groups (p=0.029). In group 1, prostate volume was 91.5% of baseline volume, whereas it was 83.1% in group 2 (Table 2). It is believed that compared with α-blocker monotherapy, monotherapy using 5-ARIs after combination therapy could reduce the risk of AUR and surgery due to prostate regrowth.

The mechanism of the prostate regrowth phenomenon after 5-ARI withdrawal is not fully understood, because the etiologies of prostate enlargement are multifactorial and complex. Because the development of BPH is an androgen-dependent process, however, it is possible that the prolonged pharmacologic inhibition of 5α-reductase, by the 5-ARIs, results in an overactivity of, or increased sensitivity to, dehydrotestosterone. An alternative mechanism might be that androgen receptors become more sensitive or upregulated during treatment with 5-ARIs. These explanations could partly account for prostate gland regrowth after discontinuing the chronic inhibition of the 5α-reductase [13].

5-ARIs, when used alone, have an onset of action of 3 to 6 months compared with 2 to 4 weeks for α-blockers [14]. Long-term therapy with a 5-ARI is maintained to reduce prostate volume and positively impact the long-term risk of BPH progression, reducing the risk of AUR and BPH-related surgery. Combination therapy can offer rapid relief of symptoms associated with α-blockers and the long-term benefits of 5-ARIs. The α-blocker would alleviate the symptoms until the 5-ARIs could reduce the obstruction, improve the symptoms, and decrease the risk of AUR and the need for outlet-reducing surgery [15]. Thus, it may not be necessary to continue the α-blocker therapy. Barkin et al reported that in men with BPH initially treated with a combination of dutasteride and tamsulosin, the α-blocker can be withdrawn in the majority of patients (77%) after 6 months [16]. Baldwin et al likewise observed that α-blocker therapy could be withdrawn in the majority of male patients (84%) after 9 or 12 months of combination therapy [17]. Nickel et al reported that finasteride monotherapy after combination therapy could sufficiently control the LUTS associated with BPH. Nickel et al also reported that the IPSS scores after 3 months of finasteride monotherapy, following a 9-month course of combination therapy with finasteride and an α-blocker, were within the criteria for equivalence to those after 9 months of combination therapy [18].

After 3 months of combination therapy, we observed that the IPSS significantly decreased by 5.3 (−29.88%) and 3.9 (−25.03%) in groups 1 and 2, respectively ($p < 0.001$). By contrast, Qmax significantly increased by 3.4 ml/s (33.78%) and 5.41 ml/s (59.54%) in groups 1 and 2, respectively ($p < 0.001$). From post-combination therapy for

3 months to post-monotherapy of either doxazosin or finasteride for 3 months, IPSS increased by 0.14 (13.03%) and 0.9 (11.94%), in groups 1 and 2, respectively. Thus, the IPSS of post-monotherapy was not significantly different from that of post-combination therapy in either group (p=0.858 and p=0.071, respectively), and the percentage change was not significantly different between the two groups (p=0.131). In group 1, Qmax decreased by 0.86 ml/s (−3.55%); thus, no change was observed (p=0.131). By contrast, in group 2, it significantly decreased by 2.22 ml/s (12.08%) (p=0.014). However, there was no significant difference in the percentage change between the two groups (p=0.200) (Table 2). When only 5-ARIs were used after the combination therapy, Qmax increased more compared with when only α-blockers were used. However, there was no considerable difference in the percentage change between the two groups, and the increase was not sufficient to exert an influence on IPSS. This suggests that shifting from combination therapy to monotherapy by using α-blockers or 5-ARIs could help to maintain the improved symptoms that were achieved by the combination therapy.

Brawer et al reported that after 54 weeks of combination therapy of α-blockers and 5-ARIs, PSA decreased by 60% or more in 31.4% of the patients, by 40% to 60% in 30.3%, by 20% to 39% in 16.8%, and by 0% to 20% in 12.8%, whereas it increased in 8.9% of the patients. However, Brawer et al reported that when the patients were monitored during 52 weeks of terazosin therapy, PSA was not affected at all [19]. Soh et al reported that α-blocker monotherapy had almost no influence on PSA even with long-term administration, and Roehrborn et al also reported that α-blockers (terazosin) did not influence PSA in BPH patients with LUTS [20, 21]. Guess et al described that after 1 year of finasteride monotherapy in BPH patients, PSA decreased by about 50% [22].

The result of our study showed that after 3 months of combination therapy, PSA decreased by 36.48% and 23.35% in groups 1 and 2, respectively. In group 1, which received doxazosin monotherapy after combination therapy, PSA increased significantly by 86.04% (p=0.002). In group 2, which received dutasteride monotherapy after combination therapy, PSA decreased by 36.35% (p=0.051) (Table 2). This indicates that α-blocker monotherapy after combination therapy with discontinuation of 5-ARIs could result in prostate volume regrowth as well as an increase in the PSA level.

Although α-blocker therapy is associated with a rapid onset of symptom relief and improvement in Qmax in men with BPH, it lacks the effect of the 5-ARIs on prostate volume. Its inability to reduce prostate volume may also account for the finding that rates of treatment failure with α-blockers are higher in men with larger (>40 cc) versus smaller prostate volumes [23,24]. Thus, in BPH patients with larger prostate volume, α-blocker monotherapy after combination therapy could not reduce the risk of AUR and prostatic surgery resulting in prostate regrowth, compared with 5-ARI monotherapy.

In this study, although α-blocker monotherapy after combination therapy could maintain the improved symptoms achieved by the combination therapy, regrowth of prostate volume was observed. Thus, this indicates that in BPH patients with moderate to severe symptoms, who have prostate volume of 30 cc or more according to TRUS, IPSS of 12 or more, and Qmax of 15 ml/s or less, α-blocker monotherapy after combination therapy is not expected to have an adverse impact on the improved symptoms from a short-term point of view, but is likely to cause adverse events such as aggravation of symptoms and AUR due to prostate regrowth from a long-term point of view.

In BPH patients with moderate to severe symptoms, 5-ARI monotherapy maintained the improved symptoms achieved by combination therapy, and no prostate regrowth was observed. In addition, the reduced PSA level achieved by the combination therapy was also maintained. Thus, 5-ARI monotherapy with discontinuation of α-blockers after combination therapy is not expected to have an adverse impact on the symptoms of patients. It is also expected to reduce the risk of AUR and surgery due to prostate regrowth.

The main limitation of this study was the short duration of the combination therapy and the short follow-up period. Short-term trials comparing combination therapy with α-blockers alone have found no significant benefits. The VA Cooperative Study and the Prospective European Doxazosion and Combination Theraphy trial demonstrated no benefit in symptoms or urinary flow rate with combination therapy versus α-blocker monotherapy after 1 year. Finasteride was shown to be no better than placebo for these outcomes [25,26]. However, the MTOPS authors concluded that long-term combination therapy significantly reduces overall clinical progression of BPH compared with monotherapy using doxazosin or finasteride. Combination therapy and finasteride alone reduced the long-term risk of AUR and the need for invasive therapy [9]. Thus, combination therapy and finasteride alone require long-term use. Several studies have demonstrated that the α-blocker can be withdrawn after an interval of combination therapy, after which symptom control is maintained with a 5-ARI alone [16-18]. The optimal duration of combination therapy seems to be around 9 months, because 84% of the men were able to discontinue α-blockers after 9 months with no increase in symptoms [27]. Because the follow-up period was short in this study, studies are required to investigate the possible impact of long-term administration on the symptoms and whether 5-ARIs could really reduce the risk of acute urinary retention and prostatic surgery. In addition, because this study is based on a single-center analysis of data, the number of patients was small and the variety of patients was low. Multi-center studies with more diverse patients are thus required.

CONCLUSIONS

In this study, in BPH patients with moderate to severe

LUTS who had prostate volumes of 30 cc or more on the basis of TRUS performed by one urologist and an IPSS of 12 or above, 5-ARI monotherapy maintained the improved IPSS and Qmax without prostate regrowth and with a reduction in the PSA level after combination therapy with an α-blocker and 5-ARI. Although the duration of drug administration was short in this study, our results suggest that in BPH patients whose symptoms improved with combination therapy, 5-ARI monotherapy could maintain the alleviated symptoms and reduce the risk of AUR and prostatic surgery due to prostate regrowth.

Conflicts of Interest

The authors have nothing to disclose.

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