Effects of alpha blocker “add on”treatment on blood pressure in symptomatic benign prostatic hyperplasia with or without concomitant hypertension

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<ABSTRACT>

Effects of alpha blocker "add on" treatment on blood pressure in symptomatic benign prostatic hyperplasia with or without concomitant hypertension

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We investigated the effects of add on treatment of alpha blocker (AB) on blood pressure (BP) and the safety of ABs in men with symptomatic benign prostatic hyperplasia (BPH) with or without hypertension. We retrospectively reviewed 2,924 BPH outpatients who took ABs at our institution between 2005 and 2009. BPH symptom severity, prostate volume, and BP were determined for 953 patients with their baseline data. BP and IPSS were measured within 2 months after AB treatment. Patients were assigned to four groups: group 1 had 272 normotensive patients with concomitant hypertensive medication; group 2 had 293 normotensive patients without the medication; group 3 had 216 hypertensive patients with concomitant medication, and group 4 had 172 hypertensive patients without the medication. The addition of AB lowered the mean systolic BP by 16.6 mmHg for group 3 and 8.6 mmHg for group 4, and diastolic BP by 18.0 mmHg for group 3 ($p<0.05$). However, normotensive groups on entry, irrespective of antihypertensive medication, showed no significant BP changes from baseline after ABs medication. In the hypertensive groups on entry, doxazosin GITS resulted in significant reductions in systolic BP from 142.2 to 134.9 mmHg and

diastolic BP from 97.6 to 84.6 mmHg. When analyzed by AB regimen, the incidence of BP-related adverse events was comparable.

AB therapy for BPH can have an appropriate and beneficial effect on BP, especially in baseline hypertensive patients. Doxazosin GITS treatment resulted in optimal management of BP within the normal range especially in the pharmacologically or physiologically hypertensive patients.

Key words : benign prostatic hyperplasia; blood pressure; alpha blocker; adverse events

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I. INTRODUCTION

Benign prostatic hyperplasia (BPH) is often encountered in aging men, and it is the most common urological disorder.[1] The prevalence of BPH and hypertension increase with age, hence both are common diseases in elderly males.[2] An estimated 25% of men aged >60 years have concomitant BPH and hypertension.[2] Although BPH and hypertension appear to involve separate disease processes, it has been postulated that age-related increases in sympathetic tone may play a role in their pathophysiologies.[2,3]

Treatments for BPH include surgical or medical therapy. The number of patients treated for BPH is rapidly increasing in Korea, and increasingly, noninvasive medical therapy is being chosen as the primary treatment option.[4] Of the medications for BPH, selective a1-adrenoceptor antagonists have been considered as an effective, noninvasive treatment option for men with BPH. However, the administration of alpha blockers to patients with BPH raises the

concern that patients who are taking other antihypertensive drugs and those with normal blood pressure (BP) could experience excessive reductions in blood pressure that would cause hypotensive symptoms. One agent that is shown to provide rapid relief is doxazosin, a selective a1-adrenoceptor antagonist that is also used to treat hypertension. Doxazosin has been shown to be effective and well tolerated in the treatment of symptomatic BPH in hypertensive patients.[5] However, previous placebo controlled study of doxazosin in normotensive BPH patients showed a decrease in BP compared to placebo.[6] Although other alpha blockers such as tamsulosin and alfuzosin are effective for treating patients with BPH and as part of combined therapy in patients with hypertension,[7,8] there are few reports comparing their effects on BP in BPH patients according to antihypertensive medication. Therefore, we aimed to retrospectively evaluate the effects of alpha blockers on BP in BPH patients with or without concomitant hypertension. We also evaluated the efficacy and safety of alpha blockers in these patients.

II. MATERIALS AND METHODS

1. Study design

We retrospectively reviewed 2,924 BPH patients who had been initially diagnosed with BPH and prescribed with α1 adrenoceptor antagonists at our institution between January 2005 and October 2009. The symptoms of BPH were collected through the routine initial evaluation of BPH using transrectal ultrasound of the prostate, uroflowmetry, International Prostate Symptom Score (IPSS), urine analysis, and prostatic specific antigen (PSA) determinations. At the initial visit, the BP and concomitant hypertension-related medication were also recorded. BP and IPSS were measured within two months after alpha blocker treatment. Hypertension was defined a diastolic BP of 90 mmHg or above in a sitting position. Adverse events (AEs) were defined as the symptoms which require discontinuation or change of the current alpha blocker medication.

2. Patients

Patients were excluded from this study if they had ever taken medications such as α-blocker or 5-alpha reductase inhibitors. Patients were also excluded if they had neurogenic bladder dysfunction, confirmed prostate cancer, acute or chronic urinary retention status, acute or chronic prostatitis within the last three months, serum prostate-specific antigen (PSA) levels over 10 ng/mL, a history of recurrent UTI or bladder stones, and previous TURP or other surgical intervention related to BPH. We also excluded the patients who were taking other antihypertensive drugs at the baseline point and until the follow up BP

measurements. Of 2,924 patients enrolled, BPH symptom severity (assessed by the International Prostatic Symptom Score [IPSS] and urinary flow rate [Qmax]), prostate volume, baseline BP (before α-blocker medication) and follow up BP (after α-blocker medication) were determined for 953 patients with the baseline data. Patients were assigned to four groups: group 1 had 272 normotensive patients with concomitant hypertensive medication; group 2 had 293 normotensive patients without the medication; group 3 had 216 hypertensive patients with concomitant medication, and group 4 had 172 hypertensive patients without the medication.

3. Statistical analysis

All analyses were conducted with SAS statistical software, version 9.1 (SAS Institute, Cary, NC). The means of the groups were compared using Student's t-test and/or ANOVA test. After performing a covarianate analysis of variance for adjusting for age and prostate volume, the significance of differences in BP among groups based on baseline BP and alpha blocker regimen was examined using two-way ANCOVA with subsequent linear contrasts. Chi square test was used to determine the statistical significance of differences in AEs among groups according to alpha blocker regimen. Differences were considered statistically significant when the probability of error was less than 5% ($P<0.05$).

III. RESULTS

The baseline characteristics of patients according to blood pressure were shown in table 1. Of 953 patients enrolled, 385 patients (40.4%) took tamsulosin 0.2mg, 203 (21.3%) alfuzosin 10mg, 197 (20.7%) doxazosin gastrointestinal therapeutic system (GITS) 4mg, and 168 (17.7%) terazosin 2mg once daily. The overall mean age was 63.2±5.8 years, and the mean prostate volume was 38.1±5.5 cc. The mean duration of follow up was 58.8±7.3 days, and there was no significant difference in the duration of follow up by alpha blocker regimen.

Table 1. The baseline characteristics of patients according to blood pressure

	Normotension		Hypertension	
	Group 1	Group 2	Group 3	Group 4
No	272	293	216	172
Age	62.8±5.7	63.3±4.4	64.2±5.8	65.9±6.1
Systolic BP (mmHg)	124.8±2.1	125.3±2.6	140.4±1.9	139.8±2.4
Diastolic BP (mm Hg)	74.5±0.9	76.2±1.0	93.1±1.2	94.4±1.3
IPSS (total)	14.7±0.5	15.6±0.5	14.8±0.3	14.2±0.4
QOL	3.5±0.2	3.6±0.5	3.7±0.4	3.0±0.5
Prostate volume (cc)	38.8±6.1	32.2±4.5	41.3±7.1	37.3±5.8
PSA (ng/ml)	2.1±0.2	1.6±0.3	1.7±0.5	2.0±0.6

Qmax (mL/s)	11.0±1.7	10.7±0.5	11.6±0.8	10.7±1.3
Residual urine volume (cc)	58.6±10.2	43.6±7.1	62.9±8.4	55.4±6.6

The values for age, blood pressure, prostate volume, PSA, IPSS, QOL, Qmax, and residual urine volume are means ± SD.

The addition of α–blockers lowered the mean systolic BP by 16.6 mmHg for group 3 and 8.6 mmHg for group 4, and diastolic BP by 18.0 mmHg for group 3 ($p<0.05$) (Fig 1). However, normotensive groups on entry, irrespective of antihypertensive medication, showed no significant BP changes from baseline values after alpha blockers medication. After adjusting for age, significant changes in the mean systolic BP from baseline values were found in group 2 (△-0.4 mmHg) versus 3 (△-16.6 mmHg), diastolic BP changes in group 1 (△+1.6 mmHg) versus group 3(△-18.0 mmHg), group 1(△+1.6 mmHg) versus group 4 (△-8.2 mmHg), group 2 (△+1.7 mmHg) versus group 3 (△-18.0 mmHg), and group 2 (△+1.7 mmHg) versus group 4 (△-8.2 mmHg) (Fig 1).

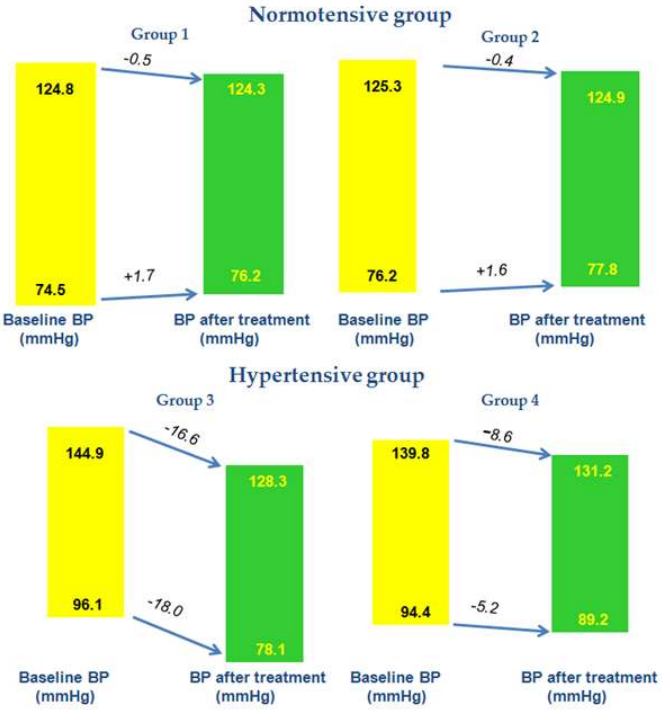

Fig 1. Comparison of the mean changes in blood pressure from baseline values according to group

The baseline and follow up BP according to alpha blocker regimen are shown in Table 2. The follow up systolic BP was only significantly lower in the doxazosin GITS treatment group. There were significant improvements in IPSS total score from baseline data for all drugs. However, there were no significant differences among drugs. Figure 2 shows the mean change from the baseline data in BP for hypertensive and normotensive patients according to alpha blocker regimen. Of the 197 patients in the doxazosin GITS group, 91 patients had the baseline high BP (53 with concurrent antihypertensive medication vs 38 without antihypertensive medication). In the baseline hypertensive BP

patients, treatment with doxazosin GITS resulted in significant reductions in systolic BP from 142.2 mmHg to 134.9 mmHg and diastolic BP from 97.6 mmHg to 84.6 mmHg (△-7.3 and △-13.0mmHg, respectively).

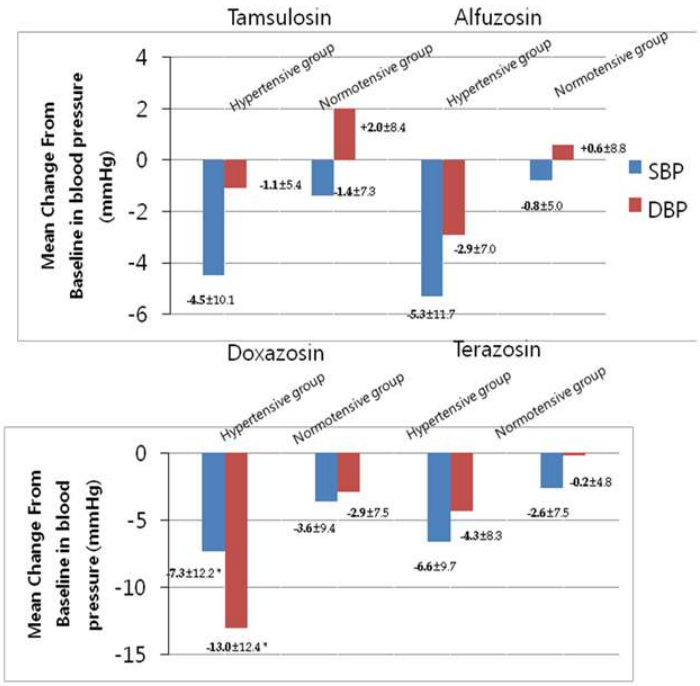

Fig 2. The mean (SD) change in BP from baseline values for hypertensive and normotensive patients according to alpha blocker regimen

Table 2. The baseline and clinical characteristics of patients according to alpha blocker regimen

	Tamsulosin 0.2 mg	Alfuzosin 10 mg	Doxazosin GITS 4mg	Terazosin 2 mg
No	385	203	197	168
Age	62.5±7.0	61.8±8.2	66.1±6.0	64.3±7.6
IPSS (total)				
Baseline	16.0±2.1*	15.5±2.6*	16.5±1.9*	15.8±2.4*
Follow up	11.6±2.0*	10.6±1.8*	12.0±1.3*	10.6±1.5*
QOL				
Baseline	3.7±0.2*	3.9±0.5*	4.0±0.4*	3.9±0.5
Follow up	3.0±0.3*	3.1±0.7*	3.3±0.6*	3.4±0.3
Prostate volume (cc)	35.8±6.1	32.2±4.5	41.3±7.1	38.3±5.8
PSA (ng/ml)	2.5±0.2	1.9±0.3	2.4±0.5	1.7±0.6
Qmax (mL/s)	11.0±1.7	11.7±0.5	10.6±0.8	10.0±1.3
Residual urine volume (cc)	60.6±10.2	51.6±7.1	67.9±8.4	62.4±6.6
Baseline BP (mmHg)				
Systolic	129.4±6.8	130.1±9.3	131.3±8.3*	129.8±7.9
Diastolic	83.6±9.2	84.5±5.9	84.9±6.7	85.8±6.2
BP following 'Add on' treatment				
Systolic	127.6±7.2	126.8±10.6	125.1±10.9*	126.2±9.1
Diastolic	83.3±9.4	84.2±8.0	83.5±6.9	84.1±7.8
Adverse events following 'Add on' treatment				
Dizziness, N(%)	11(2.2)	7(3.4)	10(5.1)	8(4.8)
Postural hypotension, N(%)	7(1.9)	5(2.5)	11(5.6)	7(4.2)
Etc., N(%)	3(0.8)	2(1.0)	2(1.0)	5(3.0)

The values for age, blood pressure, prostate volume, PSA, IPSS, QOL, Qmax, and residual urine volume are means ± SD.

* $p<0.05$ by ANCOVA test.

The incidence of BP-related side effects such as dizziness or postural hypotension was significantly higher in group 3 ($p=0.021$). When analyzed by alpha blocker regimen, the incidence of BP-related side effects was comparable, and the differences among groups

were not significant (Table 2).

IV. DISCUSSION

Because BPH and hypertension are chronic conditions, long-term medication must be safe and continuously effective during treatment. The efficacy of alpha blockers for BPH treatment has been well documented, and our results compare favorably with previous studies.[4,9,10] However, despite similar efficacy, alpha blockers have different AEs, and many AEs are secondary to reduction in blood pressure (e.g. dizziness and orthostatic hypotension) .[9] In a recent meta analysis,[11] alfuzosin, terazosin and doxazosin showed a significantly higher risk of developing vascular-related events compared with placebo, and tamsulosin showed an increase with no significance. Our previous study reported treatment with doxazosin GITS for 1 year resulted in a significantly greater reduction in BP in hypertensive patients than that in normotensive patients.[12] Furthermore, BP in the concomitant antihypertensive medication group was reduced significantly than that in the no medication group. However, in the present study, treatment with doxazosin GITS resulted in significant reductions in systolic and diastolic BP especially in the baseline hypertensive BP patients irrespective of concomitant antihypertensive medication. This contradictory findings might result from relatively small number of patients in the concomitant antihypertensive medication group (n=18) in the previous study. Our results suggests that the doxazosin GITS treatment have 'additional benefit' of lowering BP in the pharmacologically or physiologically hypertensive patients. However, we could not know why the alpha blocker "add on" treatment lowered BP, especially in baseline high BP. Our results warrant future prospective studies to elucidate the underlying mechanism.

In the present study, the overall incidence of AEs was comparable among the four groups even though systolic BP was significantly lower in the doxazosin GITS group

after doxazosin GITS add on treatment (Table 2). Because alpha blockers cause vasodilation, vascular related AEs take the form of dizziness, presyncope or syncope. These symptoms can be life threatening, particularly in an older patient population. Terazosin and doxazosin, originally developed as antihypertensive drugs, are non-subtype selective alpha 1 blockers, and both are associated with a larger number of vasodilatory side effects than either tamsulosin or alfuzosin.[13-16] In the present study, the occurrence of medication related AEs was lower than the 16.1% previously reported by Kirby et al.[17], possibly because the present study had a short term follow up period.

There are several limitations. First, it is a retrospective study with a short term follow up period. A prospective study with a long term follow up period is needed to confirm our findings. Another limitation was that the safety aspect of our study was limited to vascular related adverse events because of their potentially life threatening effects. We only identified with certainty those of sufficient severity to require discontinuation of alpha blockers. Finally, we measured blood pressure only with the patient in the seated position. We acknowledge this methodological flaw of not taking the BP in a supine position in addition to the sitting position to rule out any orthostatic hypotension that might be present. However, despite these limitations, our results provide adequate preliminary data to support a prospective, randomized, controlled trial of effect of alpha blocker 'add on' treatment on BP in patients with baseline high or normal BP.

V. CONCLUSION

Alpha blocker therapy for BPH can have an appropriate and beneficial effect on BP, especially in baseline hypertensive patients. Furthermore, doxazosin GITS treatment resulted in optimal management of BP within the normal range especially in the pharmacologically or physiologically hypertensive patients.

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< ABSTRACT(IN KOREAN)>

고혈압과 전립선 비대 동반 환자에서 알파 차단제의 장기적 효과 및 안정성

<지도교수 정 병 하>

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이 승 환

본 연구에서는 하부요로증상을 동반한 전립선 비대증 환자에서 고혈압 유무에 따라 알파차단제를 추가로 투여했을 때 하부요로증상 및 혈압에 미치는 효과와 안정성을 규명하고자 하였다. 2005년 1월부터 2009년 10월까지 전립선 비대증으로 알파차단제를 복용하였던 2,924 명의 외래 환자를 대상으로 하였으며 이중 내원 당시 하부요로 증상 정도, 전립선 크기, 혈압을 알 수 있고 추적 관찰 중 알파 차단제 투여 후 2개월 이내 혈압과 국제 전립선 증상 점수를 알 수 있었던 953명의

의무기록을 후향적으로 검토하였다. 환자군은 측정 당시 혈압 정도에 따라 4군으로 나뉘었다: 1군은 항고혈압약을 복용하면서 기초 혈압이 정상이었던 272명이었고 2군은 항고혈압약을 복용하지 않으면서 기초 혈압이 정상이었던 293명이었다. 3군은 항고혈압약을 복용하면서 기초 혈압이 고혈압으로 측정되었던 216명이었고 마지막으로 4군은 항고혈압약 복용의 기왕력이 없으면서 기초 혈압이 고혈압으로 측정되었던 172명이었다. 혈압 측정은 좌위, 와위 수축기 혈압과 이완기 혈압을 각각 측정하였으며 평균 이완기 혈압이 90mmHg 이상으로 측정하였을 때 고혈압으로 정의하였다. 3군에서 알파 차단제를 추가 투여 했을 때 평균 수축기 혈압이 16.6 mmHg 떨어졌고 4군에서는 평균 8.6 mmHg 의 혈압 저하가 관찰되었다. 또한 3군에서 이완기 혈압은 평균 18 mmHg 저하가 관찰되었으며 이는 기초 혈압에 비해 통계적으로 유의하게 떨어진 것으로 분석되었다 ($p<0.05$). 그러나 항고혈압제 복용 유무와 상관없이 기초 혈압이 정상이었던 그룹에서는 알파 차단제 투여 후에도 유의한 혈압의 변화는 관찰되지 않았다. 기초 혈압이 높았던 3군, 4군에서 doxazosin GITS (gastrointestinal therapeutic system)

약물 투여 후 수축기 혈압, 이완기 혈압 모두 142 mmHg -> 134.9 mmHg, 97.6 mmHg -> 84.6 mmHg 로 저하되었다. 그러나 알파 차단제 종류에 따라 대상군을 나누어 분석했을 때 혈압과 관련된 부작용은 유의한 차이를 보이지는 않았다. 전립선 비대증 치료제인 알파 차단제는 기초 혈압이 높았던 고혈압 환자에서 특히 혈압 강하 효과를 보였다. 또한 doxazosin GITS 약물은 전립선 비대로 인한 하부요로 증상이 있으면서 약동학적, 생리적으로 고혈압인 환자에서 특히 이점이 있을 것으로 생각된다.

핵심되는 말 : 전립선 비대증, 혈압, 알파 차단제, 부작용