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Original Article

Evaluation of the Effects of Prazosin on Resistant Diastolic Hypertension With a Focus on Sex Difference

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ABSTRACT

Background: Despite all the focus on systolic blood pressure (SBP), few studies exist on high diastolic blood pressure (DBP) treatment between the different genders. In this study, we investigated the effects of prazosin as an additional treatment for refractory DBP.

Methods: Totally, 75 nonblack adults were enrolled in this study with primary hypertension and DBP >100 mm Hg as isolated diastolic hypertension or systolic-diastolic hypertension. All the patients were treated with 1 or more drugs from the 5 major antihypertensive group drugs (ACE-I, ARB, diuretic, Ca-channel blockers, and beta-blockers). If hypertension did not respond to these drugs, prazosin was added at a mean dose of 1–2 mg (1.6 mg) daily.

Result: Many of the patients needed additional low doses of prazosin for the control of DBP. The response of the females was significantly better than that of the males to the 5 major antihypertensive drugs (P=0.001) **.**
This study showed that the 5 major drug groups, albeit conferring good SBP control (25.8% reduction in SBP), in the majority of the patients only caused a 10% decrease in DBP. However, prazosin led to a 21.8% decrease in DBP and a 9.5% decrease in SBP. Consequently, prazosin could be an effective drug in controlling resistant DBP with minimal side effects.

Conclusions: Low-dose prazosin as an additional drug to other major antihypertensive drugs with minor and transient complications can be reliably effective in reducing resistant DBP. ***(Iranian Heart Journal 2019; 20(2): 32-39)***

KEYWORDS: Resistant, HTN-diastolic, HTN-systolic

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Prazosin is an antihypertensive drug used in the second line according to the guideline (JNC 8)[1] if hypertension does not respond to other first-line drug groups (calcium-channel blockers, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blocking agent [ARBs], diuretics, and beta-blockers). For all the attention hitherto paid to systolic blood pressure (SBP), there is a dearth of data on the treatment

of high diastolic blood pressure (DBP) in the different genders. Additionally, no specific studies have evaluated uncontrolled idiopathic diastolic hypertension in patients with a normal renal function. Accordingly, we sought to study the effects of adding low-dose prazosin to other hypertensive drugs in the management of diastolic hypertension (DBP>100 mm Hg) not responding well to other antihypertensive drugs. We also compared the effects of prazosin in resistant DBP between male and female patients.

METHODS

Seventy-five nonblack nonalcoholic Iranian patients (27–70 years old) with primary hypertension and DBP> 100 mm Hg (isolated diastolic hypertension or systolic-diastolic hypertension) were studied. Patients with secondary hypertension due to renal failure, nephropathy or other organ failure were excluded from this study. All the patients were visited in our outpatient clinic for uncontrolled hypertension during a 1-year period (2016–2017).

Blood pressure (BP) was recorded by a single investigator with a manual mercury sphygmomanometer on the right arm with cuff inflation in the sitting position after 10 minutes of rest. The mean blood pressure of at least 2 measurements on 2 separate observations was recorded in mm Hg. None of the patients was on antihypertensive therapy in the preceding 6 months. All the patients maintained their ordinary diet and exercise program throughout this study.

The mean BP was calculated as (2×DBP+1×SBP)/3. Height and body weight were used to calculate the body mass index (BMI) (weight [kg] / height^2 [m]).

Statistical analysis was done using the χ^2 test or the Fisher exact test and the Mann–Whitney test. A *P* value <0.05 was considered significant.

Strategy B or C for antihypertensive drugs according to the JNC 8 was used[1]: (B strategy: Start 1 drug and then add a second drug before achieving the maximum dose of the initial drug.) and (C strategy: Begin with 2 drugs at the same time either as 2 separate pills or as a single pill combination.)

These drugs (diuretics, beta-blockers, ACEIs, ARBs, and Ca-channel blockers) were started in the first visit orally and their dose was increased gradually to control hypertension. SBP reached the target level (<140 mm Hg) in all the patients, but diastolic hypertension did not reach the target level (<90 mm Hg) in 50 patients and only 25 patients achieved the target DBP with these 5 first-line drugs.

The patients were visited at the intervals of 1 to 2 weeks. In the patients with uncontrolled diastolic hypertension after 1 month, low-dose oral prazosin was added to the other antihypertensive drugs.

In this study, information about the side effects of prazosin was given to the patients, especially first-dose postural hypotension. Almost all the patients received a diuretic for the control of SBP.

All the patients received 1 or more of the following antihypertensive drugs (5 major classes) to control systolic hypertension: hydrochlorothiazide, furosemide, atenolol, metoprolol, propranolol, captopril, enalapril, losartan, losartan-H (losartan 50 mg–12.5 mg hydrochlorothiazide), spironolacton, valsartan, and amlodipine.

After 1 month, prazosin was started in 50 patients with uncontrolled DBP at a dose of 0.5 mg at night. The patients were visited 3 days after starting prazosin to detect orthostatic hypotension (a fall of 10 mm Hg in SBP 3–5 minutes after a person assumes a standing position from a lying position).

If DBP was not controlled, the dose of prazosin was increased gradually every 1 or 2 weeks. The dose of prazosin was 0.5–5 mg once or twice daily (0.5–10 mg, mean=1–2 mg [1.6 mg/d]). Prazosin was used in this study to lower

DBP to below 90 mm Hg and the other first-line drugs were also continued without any change in their dosage.

RESULTS

Table 1 shows the patients' baseline characteristics according to response to hypertension treatment with the 5 major antihypertensive drugs.

According to Table 3, the response of the female patients to the 5 major antihypertensive drugs was better than that of the male patients (*P*=0.001), but no difference was detected based on their age differences and, overall, the response in the overweight patients was lower than that among the patients with normal weights (*P*=0.07)

Table 1. Baseline characteristics according to response to hypertension treatment with the 5 major antihypertensive drugs

Variable		Response to Treatment		Total	*P* value
		Yes	No		
Overall		25(33.3%)	50(66.7%)	75(100%)	------
Gender	Female	14(60.9%)	9(39.1%)	23(30.7%)	**0.001†**
	Male	11(21.2%)	41(78.8%)	52(69.3%)	
Age	Mean±SD	50.3 ± 8.8	52.6 ± 9.5	51.8 ± 5.8	**0.392‡**
	≤50	10(32.3%)	21(67.7%)	31(41.3%)	
	51-55	9(45%)	11(55%)	20(26.7%)	**0.370†**
	≥56	6(25%)	18(75%)	24(32%)	
BMI	Mean±SD	29.7 ± 4.2	28.8 ± 3.6	29.1 ± 3.8	**0.280‡**
	Normal	3(50%)	3(50%)	6(8%)	
	Overweight	9(22.5%)	31(77.5%)	40(53.3%)	**0.078†**
	Obesity	13(44.8%)	16(55.2%)	29(38.7%)	

† χ^2 Test or the Fisher exact test, ‡ Mann–Whitney test

In Table 2, the BP changes before and after the addition of prazosin according to age, sex, and the BMI are presented. The SBP changes had a significant correlation with age and the 5 antihypertensive drugs.The older patients had a better response to the 5 antihypertensive drugs and the mean BP change was significant in the female patients (*P*=0.032).

After the addition of prazosin, although the DBP changes were not significant between sex, age, and the BMI, the drug was able to decrease DBP, especially in the men. The SBP changes in high BMI was significant with prazosin (*P*=0.013).

Table 2 and Figure 1 compare the changes in BP between the baseline characteristics of the patients.

Side effects of prazosin in the study population

Six patients had orthostatic hypotension following the administration of the first doses, which was resolved after continuing the drug. Two patients suffered syncopal attacks after the first dose with no major trauma, which was resolved after continuing the drug. Five patients had palpitation, which required the addition of a beta-blocker (propranolol or metoral). Two patients reported headaches after the first doses. One patient reported vertigo with prazosin therapy, which was resolved after continuing the treatment. Two 2 patients discontinued prazosin due to fatigue 2 months after it was started. One neurotic female patient discontinued prazosin after 2 months due to nasal congestion and impaired taste sensation but her DBP remained controlled.

Table 2. Comparisons of the changes in blood pressure between the baseline characteristics

				After 5 Major Drugs			After Prazosin*		
BP	**Factor**	**Group**	**Before**	**After**	**Change**	***P* value**	**After**	**Change**	***P* value**
DBP	**Gender**	Male	115.6±10.8	99.0±10.2	-16.6±11.1	.134‡	80.7±5.6	-22.4±7.5	.843‡
		Female	114.7±11.6	91.9±11.9	-22.8±15.1		79.4±6.8	-24.4±11.8	
	Age	≤50	117.5±12.1	98.2±12.4	-19.3±10.5	.227†	80.7±5.9	-24.0±9.9	.755†
		51-55	116.0±12.3	94.5±11.5	-21.5±16.4		82.2±3.4	-20.9±8.0	
		≥56	112.0±7.2	97.0±9.3	-15.0±11.4		79.1±6.7	-22.5±6.5	
	BMI	Normal	115.0±10.4	91.6±9.8	-23.3±16.3	.397†	76.6±10.4	-23.3±10.4	.632†
		Overweight	115.1±9.9	98.0±9.9	-17.1±13.2		80.5±5.2	-21.7±7.2	
		Obesity	115.8±12.6	96.3±13.1	-19.4±11.1		81.2±6.2	-24.7±10.1	
		Total	115.4±10.9	96.8±11.2	-18.5±12.7		80.5±5.8	-22.8±8.3	
SBP	**Gender**	Male	179.4±23.8	133.2±8.8	-46.1±20.1	.110‡	123.0±4.4	-12.5±6.9	.250‡
		Female	181.3±22.6	128.0±10.0	-53.2±18.8		120.0±7.1	-16.6±10.3	
	Age	≤50	171.6±21.4	130.6±8.6	-40.9±20.6	.008†	120.9±5.4	-13.1±8.1	.843†
		51-55	182.0±21.4	130.2±10.8	-51.7±14.4		123.1±4.6	-14.1±8.0	
		≥56	189.1±24.3	134.1±9.1	-55.0±20.3		123.9±4.7	-13.0±7.3	
	BMI	Normal	176.6±27.3	125.8±12.8	-50.8±24.9	.678†	125.0±5.0	-11.6±2.9	.013†
		Overweight	177.2±23.2	130.8±9.2	-46.3±18.9		122.2±4.0	-10.9±6.9	
		Obesity	184.2±22.9	133.9±8.7	-50.5±20.5		122.5±6.8	-18.1±7.7	
		Total	180.0±23.3	131.6±9.4	-48.3±19.8		122.5±5.1	-13.3±7.7	
Mean BP	**Gender**	Male	136.9±10.9	110.4±8.6	-26.4±10.2	.032‡	94.8±4.4	-19.1±5.7	.691‡
		Female	136.9±10.8	103.9±10.8	-32.9±12.5		92.9±6.3	-21.8±10.4	
	Age	≤50	135.5±11.4	109.0±10.4	-26.5±10.8	.336†	94.1±5.2	-20.4±8.2	.800†
		51-55	138.0±11.4	106.4±10.5	-31.5±12.6		95.9±2.5	-18.6±6.2	
		≥56	137.7.6±9.6	109.4±8.2	-28.3±10.7		94.1±5.3	-19.3±5.2	
	BMI	Normal	135.5±10.2	103.0±10.4	-32.5±14.3	.315†	92.7±8.5	-19.4±6.7	.200†
		Overweight	135.8±10.0	108.9±8.5	-26.8±11.1		94.4±3.8	-18.1±5.5	
		Obesity	138.7±12.1	108.9±11.1	-29.8±10.9		95.0±5.9	-22.5±8.2	
		Total	136.9±10.8	108.4±9.7	-28.4±11.3		94.5±4.8	-19.6±6.7	

DBP, Diastolic blood pressure; SBP, Systolic blood pressure; BMI, Body mass index

‡ Mann–Whitney test, † Kruskal–Wallis test, * only patients treated with prazosin

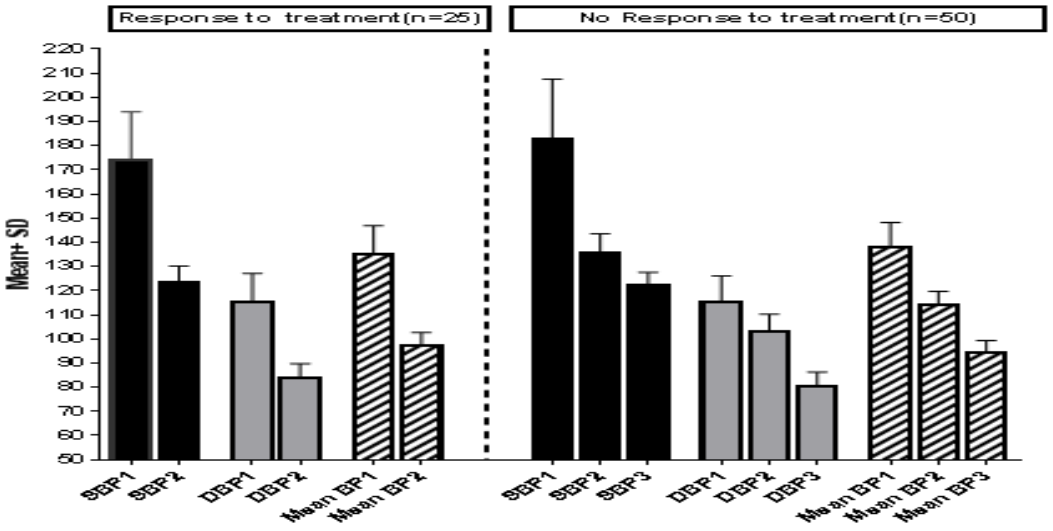

Figure 1. Changes in blood pressure (BP) according to response to hypertension treatment with the 5 major antihypertensive drugs and after prazosin therapy (BP3)

DISCUSSION

In our study, among different antihypertensive treatments, prazosin—a selective alpha receptor antagonist—effectively controlled resistant DBP, especially in male patients, while other antihypertensive agents usually controlled SBP. Previous studies have shown that prazosin decreases DBP and SBP by 10–14%. In our study, prazosin led to a 21.8% decrease in DBP and a 9.5% decrease in SBP. Therefore, we achieved a DBP <90 mm Hg with prazosin with no side effects at 12 months' follow-up.

The effects of single or combination therapy with prazosin on controlling hypertension have been shown for decades; however, the effects of single therapy are less than those of combination therapy.[2,3] Moreover, single therapy is mainly effective in mild-to-moderate hypertension.[4]

In previous studies, besides prazosin, adding other alpha-blockers like doxazosin to other antihypertensive drugs resulted in the optimal control of BP in patients with resistant hypertension defined as failure of BP control despite treatment with 3 drugs, including diuretics.[5,6]

Many studies have shown the favorable metabolic effects of alpha-blockers in antihypertensive regimens.[7] In a study by Takao Saruta,[8] prazosin increased HDL-cholesterol, inhibited the elevations of total cholesterol, and decreased triglycerides when administered in low doses in hypertensive patients.

A study showed that alpha (1)-adrenoceptor antagonists like doxazosin were useful in hypertensive patients who had hyperlipidemia, benign prostatic hyperplasia, pheochromocytoma, and hypertensive chronic cerebral infarction.[9] It has also been reported that prazosin with its vasodilatory effects is useful in severe congestive heart failure through inducing a sustained decrease in both cardiac preload and impedance.[10]

According to a previous study, adding 4 mg of extended–release doxazosin at night to multi-drug antihypertensive therapy improves cardiovascular autonomic control, increases heart-rate variability, controls SBP and DBP, and decreases pulse pressure.[11]

Frans et al[12] reported the effects of prazosin on the regression of ventricular hypertrophy, which is effective in the prognosis of hypertensive patients, as compared with hydralazine.

The effects of prazosin on controlling BP in chronic renal failure and kidney transplantation patients have been well established.[13] Furthermore, a group of patients with hypertension who use 2 or more drugs like diuretics or ACE inhibitors for hypertension control gradually develop some degrees of mild renal insufficiency, which highlights the importance of prazosin. The focus of our study was on high grades of resistant diastolic hypertension (≥110 mm Hg) in patients without renal or other organs failure. The SBP of all the patients was controlled with treatment regimens recommended in relevant guidelines, while their DBP was not controlled in 50 out of 75 patients.

In a study by Han et al,[14] beta-blockers and ACE inhibitors were effective in controlling isolated diastolic hypertension and thiazide and calcium-channel blocker were effective in systolic/diastolic hypertension; nonetheless, in our study, DBP was not controlled in the majority of the patients (50 from 70) with these major first-line drugs.

A previous study showed that alpha-adrenoceptor blockade with prazosin reversed cardiac remodeling and ameliorated subcellular defects in heart failure due to myocardial infarction.[15]

Further, previous studies have shown that it is easier to control DBP than SBP.[16,17] In our study, DBP was not controlled with major antihypertensive drugs in 50 of 75 patients, in whom prazosin was used, despite SBP control. The reason for the difference could be that the

patients mostly had diastolic hypertension >110 mm Hg and only 6 out of 50 patients had DBP <110 mm Hg, whereas in previous studies, DBP was mainly less than these values.

In our study, it was much harder to control high-grade diastolic hypertension than systolic hypertension in men and it was easier to achieve better control in women. In this study, patients with uncontrolled resistant diastolic hypertension were mostly men. This finding can be explained by the hormonal effects of androgen in men and the known effects of this hormone on activating the renin-angiotensin system and the subsequent increase in vascular resistance.[18,19] Prazosin decreases vascular resistance as an alpha-blocker. The patients whose DBP was controlled without prazosin were mostly women, and the reason could be the hormonal effect and more stress in women.

In our study, adding low-dose prazosin to other antihypertensive regimens caused a reduction in DBP to the target level. Prazosin was administered at a mean dose of 1–2 mg (1.6 mg) daily in our study, starting from a dose of 0.5 mg oral at bedtime that increased gradually to 0.5–10mg daily.

First-dose phenomenon with prazosin, which means orthostatic hypotension or syncope following the administration of the first dose of prazosin, has been reported in previous clinical studies mostly with higher doses and in combination with other antihypertensive drugs. We used low-dose prazosin in this study. Low-dose prazosin was started at night with no major side effects, especially syncope and orthostatic hypotension.

Of 50 patients that received prazosin, 6 had orthostatic hypotension following the first doses, which was resolved after continuing the drug. Two patients suffered syncopal attacks with the first dose with no major trauma, which was resolved after continuing the drug. Five patients, who were mostly young (<45 years of age), had palpitation, which required the addition of a beta-blocker (propranolol or metoral). Two patients reported headaches in the first doses. One patient reported vertigo with prazosin therapy, which was resolved after continuing the therapy. Two patients discontinued prazosin due to fatigue 2 months after it was started; DBP in these patients increased. One neurotic female patient discontinued prazosin after 2 months due to nasal congestion and impaired taste sensation but her DBP remained controlled.

In our study, if a patient discontinued prazosin, DBP increased during the 12-month follow-up. The only exception was the neurotic woman, in whom DBP did not increase after discontinuing prazosin. We had no cases of fluid retention as a side effect of prazosin.

Orthostatic hypotension is the most common side effect of prazosin that is mainly observed following the administration of the first dose of this drug. The following hints reduce the likelihood of its occurrence: using low-dose prazosin, taking the first dose just before sleeping, attention to the simultaneous use of diuretics, no sildenafil administration, and using prazosin in the first line of treatment.[20] Renal failure, bradyarrhythmia, diabetes, hyperlipidemia, hyperuricemia, bronchospasm, and erectile dysfunction, which may be seen or exacerbated with other antihypertensive agents, are rare with prazosin.[21] Prazosin is, therefore, considered a safe option in this situation.

Since DBP is directly associated with vascular resistance and inversely associated with pulse pressure, prazosin and other selective alpha-blockers like terazosin have an important role in the prognosis of cardiovascular and hypertensive patients through decreasing the vascular resistance and increasing pulse pressure.[18]

Careful control of BP is very important in decreasing cardiovascular mortality and most hypertensive patients need 2 or more drugs to control their blood pressure.[22] Thus, is important to select drug combinations with minimal side effects to control DBP. Men have higher BP than do women at the same age due to the blunting of the pressure-natriuresis

relationship, high androgen and renin-angiotensin system; nonetheless, post menopause, women mostly have higher BP than do men mostly due to the loss of estrogen.[19]

CONCLUSIONS

In our study, prazosin was an effective drug in controlling resistant DBP with minimal side effects besides other antihypertensive regimens, especially in male patients. More attention should be paid to adding this drug to the main antihypertensive drugs in the first line of treatment of high-grade diastolic hypertension in special groups of patients like those with metabolic disorders, hyperglycemia, hyperlipidemia, benign prostatic hyperplasia, and erectile dysfunction, as well as patients with cardiac failure, bradyarrhythmia, renal failure, and renal transplantation.

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