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Original Paper

Pulse Pressure Is Useful for Determining the Choice of Antihypertensive Drugs in Postmenopausal Women

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Key Words

Pulse pressure · Angiotensin receptor blocker · Calcium channel blocker · Diuretic · $\alpha\beta$ -Blocker

Abstract

Objective: To assess the efficacy of various classes of antihypertensive drugs in postmenopausal women with hypertension using pulse pressure (PP) as an index. **Patients and Methods:** Selected women were required to be naturally menopausal for at least 1 year but not more than 5 years past their menstrual period. Exclusion criteria were a history of preeclampsia or eclampsia, a severe illness such as myocardial infarction or stroke within 6 months, the use of estrogens or progestins within 3 months, proteinuric nephropathy, and surgically induced menopause. There were 114 women who participated in this study after having given informed consent. These women were diagnosed as having hypertension based on an office blood pressure $>140/90$ mm Hg as well as a self-measured blood pressure at home $>130/85$ mm Hg. If both levels of blood pressure were not fulfilled, the patients were excluded. All antihypertensive medications were withdrawn 6 weeks before the initiation of the study. The patients were randomly assigned in equal numbers to the following groups: (1) combination therapy with losartan (angiotensin receptor blocker) 50 mg daily + trichlormethiazide (diuretic) 2 mg twice a week, and (2) combination therapy with cilnidipine (calcium channel blocker) 5 mg + arotinolol ($\alpha\beta$ -blocker) 10 mg daily. **Results:** The patients were retrospectively divided into three groups according to their PP at the start of the study: Group I ($n = 24$), >65 mm Hg; Group II ($n = 58$), $65\text{--}45$ mm Hg, and Group III ($n = 32$), <45 mm Hg. In Group I, combination therapy with cilnidipine + arotinolol resulted in a greater reduction in the systolic blood pressure than the combination therapy with losartan + trichlormethiazide (from $169/88 \pm 2/5$ to $133/73 \pm 2/5$ mm Hg vs. from $169/88 \pm 2/5$ to $149/66 \pm 2/5$ mm Hg, $p < 0.05$). On the other

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hand, in Group III, losartan + trichlormethiazide decreased diastolic as well as systolic blood pressures (from $152/106 \pm 2/2$ to $123/78 \pm 1/1$ mm Hg vs. from $149/107 \pm 2/2$ to $129/84 \pm 2/1$ mm Hg, $p < 0.05$). In Group II, there were no differences between the two antihypertensive regimens. Laboratory findings were not influenced by any type of treatment. **Conclusions:** PP measurement before starting medication for hypertension may be useful for determining the choice of antihypertensive drugs.

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Introduction

By the age of 55 years, when most women have reached menopause, they begin to have a higher blood pressure. Although the results of studies published in the literature so far are contradictory, there is some evidence suggesting that the higher incidence of hypertension after menopause may not be solely due to the increasing age but may also be the result of a greater steepness of the age-related blood pressure increase around the menopausal period [1, 2]. Moreover, menopause per se has been suggested to potentiate the age-related increase in systolic blood pressure (SBP) [3]. An increased pulse pressure (PP) and a decreased diastolic blood pressure (DBP), in association with an elevated SBP, are superior risk markers of hypertensive cardiovascular disease in middle-aged and older subjects, as both large artery stiffness and peripheral vascular resistance are fully represented by these blood pressure indices [4–6]. Moreover, despite similar reductions in peripheral blood pressure, different cardiovascular outcomes between different classes could be due to their variable effects on PP [7, 8].

Currently, it is often necessary to combine two or more antihypertensive agents in many patients with hypertension to reach blood pressure goals [9]. A careful selection of combination therapies with low doses of antihypertensive drugs can facilitate good blood pressure control without adverse effects and may even offer the potential for improving quality of life measures during therapy [10–12].

The main objective of this study was to determine whether a patient's best drug could be predicted by a range of baseline measurements and whether interindividual variability in response was itself quantifiable [13] in postmenopausal women with hypertension. Since it has been suggested that a combination of antihypertensive drugs with and without vasodilating actions might be appropriate for the treatment of hypertension, two combinations were selected: (1) losartan, an angiotensin receptor blocker (ARB), combined with trichlormethiazide, a diuretic, and (2) cilnidipine, a calcium channel blocker (CCB) with the ability to inhibit the activity of the sympathetic nervous system, combined with arotinolol, an α -blocker.

Subjects and Methods

Selected women were required to be naturally menopausal for at least 1 year but not more than 5 years past their menstrual period. Exclusion criteria were a history of preeclampsia or eclampsia, a severe illness such as myocardial infarction or stroke within 6 months, the use of estrogens or progestins within 3 months, proteinuric nephropathy, and surgically induced menopause. There were 114 women who participated in this study after having given their informed consent. These women were diagnosed as having hypertension based on an office blood pressure $>140/90$ mm Hg as well as on a self-measured blood pressure at home $>130/85$ mm Hg, or the patients were taking any kind of antihypertensive drugs. If both levels of blood pressure were not fulfilled, the patients were excluded. All antihypertensive medications were withdrawn 6 weeks before the initiation of the study. The patients were randomly assigned in equal numbers to the following groups: (1) losartan 50 mg daily + trichlormethiazide 2 mg twice a week, and (2) cilnidipine [14]

Table 1. Baseline demographic and clinical characteristics of postmenopausal hypertensive women in the two treatment groups

Parameters	Losartan + trichlormethiazide	Cilnidipine + arotinolol
Age, years	52.3±2	52.5±2
Body mass index	24.3±1.2	24.5±1.1
Total cholesterol, mg/dl	225±12	230±8
Fasting glucose, mg/dl	112±6	110±7
Values represent mean ± SD.		

5 mg + arotinolol 10 mg daily. During the 2 weeks prior to the start of the antihypertensive medications, blood pressure measurements in the office and at home were repeated at least twice. Each treatment schedule was continued for 3 months. Blood pressure and heart rate were measured in triplicate with the same oscillometric monitor at each visit after sitting for 10 min. Blood samples for routine laboratory tests were obtained after seated for at least 15 min. The visits were scheduled in the afternoon, and the visit time was the same for each patient. Adverse events were recorded by means of a standard questionnaire.

The treatment response was evaluated in terms of absolute values of blood pressure at the completion of the study. If a patient's blood pressure was <140/90 mm Hg, the patient was considered a responder to the treatment. If the patient's blood pressure was >140/90 mm Hg, the patient was considered a nonresponder to the treatment.

Statistical Analysis

The results are reported as mean ± standard error of the mean. Analysis of variance for repeated measures, followed by the Newman-Keuls test as a post hoc test, was used for statistical analysis. $p < 0.05$ was considered significant. The data from blood pressure measurements of each patient were pooled.

Results

Patient Characteristics

Table 1 displays the baseline demographics of the patients enrolled in this study. There were no significant differences between the two groups.

Efficacy Based on Change in Blood Pressure

Figure 1 shows the effects of both treatments on blood pressure for 3 months. Both treatments significantly decreased SBP and DBP at the end of this period.

The patients were retrospectively divided into three groups according to their PP at the start of the study: Group I ($n = 24$), >65 mm Hg (fig. 2); Group II ($n = 58$), 65–45 mm Hg (fig. 3), and Group III ($n = 32$), <45 mm Hg (fig. 4). In Group I, the combination therapy with cilnidipine and arotinolol resulted in a greater reduction in SBP and DBP than the combination therapy with losartan and trichlormethiazide (from $169/88 \pm 2/5$ to $133/73 \pm 2/5$ mm Hg vs. from $169/88 \pm 2/5$ to $149/66 \pm 2/5$ mm Hg, $p < 0.05$). On the other hand, in Group III, the drug combination effect was reversed in that losartan + trichlormethiazide caused greater reductions in DBP and SBP (from $152/106 \pm 2/2$ to $123/78 \pm 1/1$ mm Hg vs. from $149/107 \pm 2/2$ to $129/84 \pm 2/1$ mm Hg, $p < 0.05$) than cilnidipine + arotinolol. In Group II, while one drug combination was not better than the other, both were effective in reducing the baseline SBP and DBP levels at 1, 2, and 3 months.

Efficacy Based on Percentage of Responders

The percentages of responders to the combination therapies with losartan + trichlormethiazide and cilnidipine + arotinolol were 0 and 100% in Group I, 90 and 85% in Group II, and

Fig. 1. Effects of the combination therapies with losartan 50 mg daily + trichlormethiazide 2 mg twice a week (n = 57) and with cilnidipine 5 mg + arotinolol 10 mg daily (n = 57) on both SBP and DBP of the patients. # p < 0.01 compared to the baseline values.

Fig. 2. Effects of the combination therapies with losartan 50 mg daily + trichlormethiazide 2 mg twice a week (n = 12) and with cilnidipine 5 mg + arotinolol 10 mg daily (n = 12) on both SBP and DBP of the patients with a relatively wider PP (Group I). # p < 0.01 compared to the baseline values; * p < 0.01 cilnidipine group compared to losartan group.

100 and 100% in Group III. In Group I, there was a significant difference between the two treatment regimens for SBP at 1, 2, and 3 months. For DBP, significance was only shown at 2 months. In Group III, the differences between the drug combinations were significant only at 2 months. In Group II, as stated earlier, there were no differences between the two drug combinations at any of the times.

Fig. 3. Effects of the combination therapies with losartan 50 mg daily + trichlormethiazide 2 mg twice a week (n = 29) and with cilnidipine 5 mg + arotinolol 10 mg daily (n = 29) on both SBP and DBP of the patients with a standard PP (Group II). # p < 0.01 compared to the baseline values.

Fig. 4. Effects of the combination therapies with losartan 50 mg daily + trichlormethiazide 2 mg twice a week (n = 16) and with cilnidipine 5 mg + arotinolol 10 mg daily (n = 16) on both SBP and DBP of patients with a relatively narrow PP (Group III). # p < 0.01 compared to the baseline values. * p < 0.01 cilnidipine group compared to losartan group.

Changes in PP

The changes in PP are summarized in table 2. In the patients with a wider PP, the combination therapy with cilnidipine and arotinolol resulted in a significantly narrower PP than the combination therapy with losartan and trichlormethiazide. In contrast, in the patients who had a narrower PP, the combination treatment with losartan and trichlormethiazide made the PP significantly narrower than the combination treatment with cilnidipine and arotinolol.

Table 2. Changes in PP in Group I (>65 mm Hg), Group II (65–45 mm Hg) and Group III (<45 mm Hg)

		Before	After 3 months
I	A	81±14	79±14
	B	81±14	67±14*
II	A	58±6	54±6
	B	57±6	53±6
III	A	44±2	35±2*
	B	43±2	45±2

Values represent mean ± SD. A: combination of losartan and trichlormethiazide; B: combination of cilnidipine and arotinolol.

* p < 0.05.

Table 3. Changes in heart rate in Group I (>65 mm Hg), Group II (65–45 mm Hg) and Group III (<45 mm Hg)

		Before	After 1 month	After 3 months
I	A	76±5	76±6	75±3
	B	75±5	75±4	75±4
II	A	69±6	65±4	67±5
	B	75±5	71±2	71±3
III	A	69±4	68±4	68±5
	B	68±6	65±5	68±4

Values represent mean ± SD. A: combination of losartan and trichlormethiazide; B: combination of cilnidipine and arotinolol.

Changes in Heart Rate

The changes in heart rate are given in table 3. In the patients of each group, the combination treatment with cilnidipine and arotinolol resulted in a slower heart rate than at baseline (not significant). The combination of losartan and trichlormethiazide showed similar results except for the patients in Group III.

Adverse Effects

None of the patients dropped out of the study and no serious adverse events were reported throughout the study. Four patients treated with cilnidipine + arotinolol and 2 patients treated with losartan + trichlormethiazide had complaints of mild headache, which was probably due to the sudden reduction in their blood pressure. Transient suspension of antihypertensive treatment relieved these complaints and the patients were able to return to the study protocol.

Discussion

The present study has shown that the level of PP at the start of an antihypertensive therapy influences blood pressure reduction in postmenopausal women with hypertension. In women with a wider PP, the combination with a CCB and an $\alpha\beta$ -blocker produced a greater reduction in blood pressure and a higher responder rate than in women with a narrower PP.

On the contrary, in women with a narrower PP, the combination of an ARB and a diuretic induced a greater reduction in blood pressure than in women with a wider PP. It is suggested that the menopause, by increasing the stiffness of the aorta, may contribute to the rise in SBP and PP that occurs in middle-aged women. However, in the present study, not all postmenopausal women with hypertension experienced an increase in SBP and PP. The percentage of a PP >65 mm Hg was 21%, that of a normal PP ranging from 65 to 45 mm Hg was 50%, and that of a PP <45 mm Hg was 28%. This is partly due to a mixture of subjects who were hypertensive before the cessation of their menstruation and of those who became hypertensive during the transition from a regular menstrual cycle to ovarian failure. Or, as explained by Staessen et al. [15] in a cross-sectional study, it is reflected by the fact that the menopause is accompanied by a steeper rise in SBP with age as well as by an increase in the absolute level of DBP. Another important factor is obesity in postmenopausal women. Shelley et al. [16] reported in a longitudinal study that DBP increases as the body mass index increases during menopausal transition. However, the present study showed that women who were already postmenopausal had the least gain in BMI. It is therefore unlikely that a gain in body weight influences blood pressure changes. The principles of the treatment of hypertension in menopausal women also apply to other women as well as to men [17].

The choice of antihypertensive drugs in postmenopausal women should be made based on the results of clinical trials specifically aimed at hypertension in these patients and should be focused on their safety, tolerability, and efficacy. The Moexipril as Anti-hypertensive Drug After Menopause (MADAM) program is a series of trials to test whether or not the drug could be indicated specifically for hypertensive menopausal women. In patients with moderately severe essential hypertension, moexipril, an angiotensin-converting enzyme (ACE) inhibitor, was as effective as hydrochlorothiazide, a diuretic, and the benefit was additive when the drugs were given together [18]. In 97 postmenopausal women with a DBP of 95–114 mm Hg while seated, both moexipril and hydrochlorothiazide were satisfactory in reducing blood pressure. In this MADAM study, the adverse effects reported for the 25-mg dose of hydrochlorothiazide were significant increases in serum uric acid, plasma glucose, and total cholesterol/high-density lipoprotein (HDL) ratio, and a significant decrease in HDL. Losartan, which was employed in the present study, increases the excretion of urate after dosing. It has been reported that serum uric acid was significantly reduced after 21 days of therapy in patients with thiazide-induced asymptomatic hyperuricemia [19]. In addition to these advantages, losartan is neutral in its effect on lipid and glucose metabolisms [20]. On the grounds of these reports, we employed the combination therapy with losartan and trichlormethiazide for the treatment of hypertension in postmenopausal women. Contrary to the favorable reputation of ACE inhibitors and ARBs, the role of CCBs for the treatment of hypertension has been a matter of debate [15, 21, 22]. Dickerson et al. [13] proposed the A (ACE inhibitors) B (β -blockers)/C (CCBs) D (diuretics) rule on choosing a drug combination for the treatment of essential hypertension because of a marked variability in the responses of hypertensive patients to different antihypertensive drugs. According to this rule, if an $\alpha\beta$ -blocker was selected, a CCB or a diuretic would be preferred as an additive drug in the combination. In our previous reports [23, 24], the combination therapy with a CCB and an $\alpha\beta$ -blocker was shown to be effective in both the reduction in blood pressure and the protection of target organ damage in patients with renal impairment. These data will be applicable for postmenopausal women with hypertension who have been considered to have a higher risk of atherosclerosis and cardiovascular events [25].

In the present study, we compared the efficacy of blood pressure reduction and the safety of combination therapy using an ARB with a diuretic as well as a CCB with an $\alpha\beta$ -blocker in postmenopausal women with hypertension. The results of this study show that both combination therapies are effective in significantly reducing blood pressure in hypertensive post-

menopausal women. However, there was a significant difference between the two combination treatments. SBP was mainly influenced by ventricular ejection, arterial stiffness, and the timing of wave reflection, while DBP was influenced by arterial stiffness and peripheral vascular resistance. Antihypertensive drugs can decrease PP by changing the amplitude and timing of reflected waves through various mechanisms. β -Adrenoreceptor antagonists can decrease arterial PP by changing the characteristics of left ventricular ejection. ACE inhibitors are known to improve large-artery compliance in hypertensive patients. In the present study, we administered a fixed dose of antihypertensive drugs instead of achieving a target blood pressure. Combination therapy for hypertensive patients would be recommended for several reasons. One major reason is that many factors are considered to contribute to blood pressure elevation in essential hypertension. In addition, combination therapy would cancel adverse effects that are produced by monotherapy treatment. In women who had systolic hypertension, the combination therapy with cilnidipine and arotinolol produced a greater reduction in PP than the combination therapy with losartan and trichlormethiazide. In the present study, we did not measure the patients' aortic peak flow, but the literature suggests that some β -blockers reduce the aortic peak flow, which in turn influences PP. Moreover, combination therapy would potentiate the antihypertensive action of the partner drug. In the present study, two kinds of combination treatment were employed. One was the combination of an ARB and a diuretic. Diuretics are known to potentiate the antihypertensive and antiproteinuric effects of ARBs. Moreover, losartan can cancel hyperuricemia induced by diuretics. The other combination used a CCB and an $\alpha\beta$ -blocker.

Two recent issues should be mentioned. First, the NICE guideline from a British study [26] excludes β -blockers from the first-line drugs. In the present study, our plan was based on the previous guideline. However, we believe an $\alpha\beta$ -blocker is effective for postmenopausal women in reducing higher heart rate, which is frequently seen in this population. Second, PP was used as an index in the present study. This is supported by a recent study by Regnault et al. [27] who showed that the attenuation of PP amplification in postmenopausal women contributes to a significant increase in cardiovascular disease risk. It remains to be seen whether these findings also apply to patient populations other than postmenopausal women. However, large long-term clinical trials of antihypertensive treatment have included both men and women and have not demonstrated clinically significant sex differences in blood pressure response and outcomes [28].

In conclusion, it is suggested from this study that the measurement of PP before starting medication of hypertension may be useful for determining the choice of the antihypertensive drugs.

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