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Research Article
Effect of Amlodipine, Benidipine and Lercanidipine Monotherapy on Pulse Pressure: A Sub-Group Analysis of the Large HYT Survey

[1,2]Fici Francesco, [3]Topaloglu Caner, [3]Tengiz İstemihan, [4]Robles Roberto Nicolas, [5]Arı Elif, [6]Arican Tarim Bahar, [7]Faikoglu Gokhan, [7]Saygısever-Faikoglu Kübra, [8]Uskur Tugce and [9]Grassi Guido

[1]Department of Cardiovascular Risk, Salamanca University, Salamanca, Spain
[2]Department of Cardiovascular Risk, Milano-Bicocca University, 20126 Milano, Italy
[3]Department of Cardiology Medical Park Hospital, Izmir University, Izmir, Turkey
[4]Department of Nephrology, Hospital University of Badajoz, Badajoz, Spain
[5]Department of Nephrology, Health Sciences University, Istanbul, Turkey
[6]Department of Internal Medicine, Kartal Research and Education Hospital, Istanbul, Turkey
[7]Department of Medical Pharmacology, University Cerrahpasa, Istanbul, Turkey
[8]Department of Medical Pharmacology, Faculty of Medicine, Kırklareli University, Kırklareli, Turkey
[9]Department of Medicine and Surgery, Faculty of Medical Clinics, University of Milano-Bicocca, Milano, Italy

Abstract

Background and Objective: High blood pressure (BP) in elderly patients is associated with arterial stiffness, which in turn increases central SBP and pulse pressure (PP). The PP, assessed with accurate methods or as brachial SBP-DBP (bPP), triggers target organ damage and cardiovascular outcomes. Considering this relationship, PP is an important treatment target. Dihydropyridine calcium blockers and renin-angiotensin-aldosterone inhibitors decrease, both, brachial and central PP. The aim of this study was to evaluate the changes in bPP obtained in hypertensive patients. **Materials and Methods:** The hypertensive patients were treated for 6 months, with amlodipine, (10 mg/day), benidipine (8 mg/day) and lercanidipine (10 mg/day). Pulse pressure, blood pressure, blood pressure control values of lercanidipine, benidipine and amlodipine groups were compared. The statistical analysis of the data was performed using the software (SAS version 9.0). A value of $p<0.05$ was considered statistically significant. **Results:** At the end of the follow-up, bPP was decreased by 8.9 mm Hg with amlodipine, 7.0 mm Hg with benidipine and 10.6 mm Hg with lercanidipine, with a statistically significant difference between benidipine and both amlodipine and lercanidipine ($p<0.05$). No significant difference was obtained between amlodipine and lercanidipine. All the drugs also lowered BP, however, amlodipine and benidipine, decreased less than lercanidipine SBP ($p<0.05$). **Conclusion:** Current results suggested a lesser potential cardioprotective effect of benidipine, compared with amlodipine and lercanidipine.

Key words: Pulse pressure, blood pressure, lercanidipine, benidipine, amlodipine

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Corresponding Author: Faikoglu Gokhan, Department of Medical Pharmacology, University Cerrahpasa, Istanbul, Turkey

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Pulse pressure (BP) is determined by the complex relationship of maximum aortic blood flow, aortic elasticity, cardiac stroke volume and peripheral vascular tension. It is obtained by subtracting the diastolic blood pressure from the systolic blood pressure. The hardening occurring in the arterial vascular structure increases systolic blood pressure and decreases diastolic blood pressure, resulting in a significant increase in pulse pressure[1-4]. Increased pulse pressure is associated with increased cardiovascular risk in various disease groups.

Studies have found that an increase in pulse pressure is closely linked to an increase in afterload, myocardial oxygen requirement, subendocardial ischemia and impaired ventricular relaxation[5,6].

There are several studies evaluating drug therapy for HF and hypertension, specifically those that reduce pulse pressure and arterial stiffness. Preliminary data from experimental and clinical studies support that ACE inhibitors and Calcium Channel Blockers (CCBs) increase arterial compliance. Considering the relationship between PP (central or brachial) and the risk of cardiovascular events, PP is an important treatment target, particularly in hypertensive patients. Antihypertensive agents reduce both SBP and DBP, but Dihydropyridine Calcium Blockers (DH-CCBs) and Renin-Angiotensin-Aldosterone (RAAS) inhibitors that decrease both brachial and central pressure[7-12], therefore are the most effective drugs to improve the hemodynamic effect of arterial stiffness.

The aim of the current study was to evaluate the changes in bPP, from the results of the HYT survey.

MATERIALS AND METHODS

Study area: The study was carried out in Turkey between 2012 and 2013, with the coordinator center being Istanbul University, Faculty of Medicine.

Study design: The HYT-HYperTension survey[13], was a cross-sectional study, that included 7310 hypertensive outpatients, treated with DH-CCBs, either as monotherapy or in combination with inhibitors of RAAS. The study patients were distributed in 3 groups, group 1: Amlodipine (n = 920), group 2: Benidipine (n = 153) while, group 3: Lercanidipine (n = 1156) were homogeneous regarding age, gender, weight, body mass index (BMI), diabetes, kidney and cardiovascular (CV) disease, BP and bPP values. Demographics and clinical characteristics of patients were reported in Table 1.

From patients treated with DH-CCBs, as mono-therapy, 2228 signed the informed consent to continue the same treatment for 6 months and have been assigned to: Amlodipine, (10 mg/daily), benidipine (8 mg/daily) and lercanidipine (10 mg /daily).

Patients were excluded if they had secondary hypertension or previous cardiovascular or cerebrovascular disease, such as myocardial infarction, unstable angina, heart failure, serious arrhythmia and hepatic or renal dysfunction.

The primary measured parameter was the changes in bPP, calculated as brachial SBP-DBP, at the end of the follow-up. The secondary measured parameters were the reduction of BP values and the rate of patients with BP control (BP<140/90). Blood pressure was measured in a sitting position and the average of 2 measurements was considered for the statistical analysis.

Ethical consideration: The study method was designed to retrospectively examine patient data between 2012-2013. This retrospective study does not require ethics committee approval.

Statistical analysis: Statistical analysis was performed per protocol using the software (SAS version 9.0). The distribution of data was tested using the Kolmogorov-Smirnov Test. Continuous variables were compared with ANOVA, with Bonferroni correction, or paired t-Test and categorical variables with the Chi-square Test. Two-sided $p<0.05$ were considered statistically significant.

RESULTS

Of the 2229 hypertensive patients who signed the informed consent, 1072 were not included in the analysis because 598 did not return at the end of the follow-up, 299 withdrew their consent and 175 for incomplete data. Therefore, this study was completed with 6 month treatment protocol with 1157 patients, whose information was in Table 1.

Average pulse pressure: The changes in the average pulse pressure values of the patients receiving treatment before and after the treatment were shown in Fig. 1. After treatment, there was a statistically significant difference in pulse pressures between the three treatment groups ($p<0.05$). As a result of the Bonferroni Test performed to determine which treatment groups caused this significant difference, it was determined that this difference was caused by amlodipine and benidipine and benidipine and lercanidipine treatments.

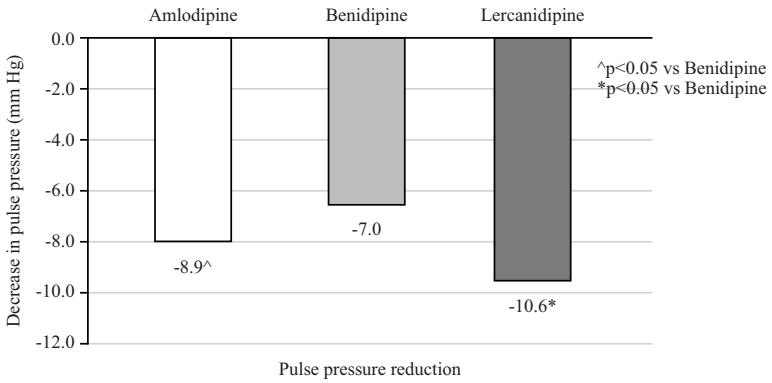

Fig. 1: Changes in the average pulse pressure values of the patients receiving treatment
A statistically significant difference in pulse pressures between the three treatment groups (p<0.05)

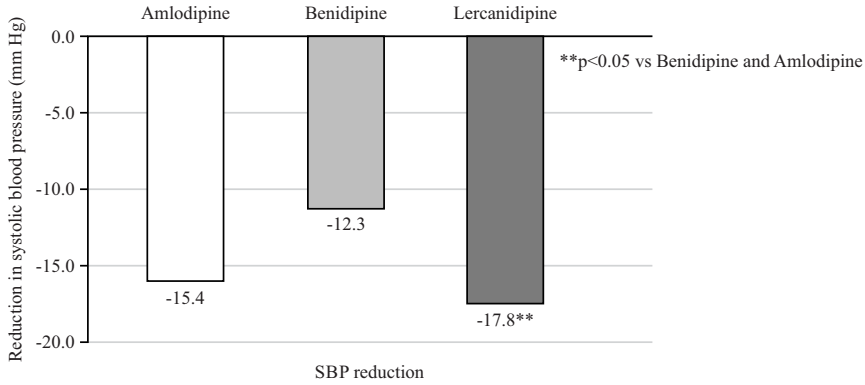

Fig. 2: Distribution of the decrease in systolic blood pressure
A statistically significant difference was observed at (p<0.05)

Table 1: Demographic and clinical characteristics of patients at baseline

	Amlodipine (n = 920)	Benidipine (n = 153)	Lercanidipine (n = 1156)	p-value
Males (%)	58.2	60.4	60.8	0.18
Age (year)	60.9±11.6	61.3±11.4	60.8±11.6	0.75
Weight (kg)	79.8±13.4	80.1±12.6	80.6±13.4	0.22
BMI (kg m^{-2})	29.9±5.1	29.9±5.0	30.1±5.1	0.59
SBP (mm Hg)	143.6±15.8	144.1±10.1	145.1±16.9	0.31
DBP (mm Hg)	87.6±8.2	87.0±9.0	88.2±5.8	0.60
Pulse pressure (mm Hg)	56.1±14.0	57.1±14.8	56.9±14.5	0.62
Diabetes (%)	23.2	23.8	20.6	0.31
Renal disease (%)	2.6	2.6	2.0	0.20
CV disease (%)	19.0	22.4	20.2	0 55

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure and CV: Cardiovascular

When the changes in the patients pulse pressures before and after treatment were examined, it was determined that there was a decrease in all treatments after the treatment compared to before and these decreases were statistically significant (p<0.05). After the treatment, there was a statistically significant decrease in the pulse pressure values in all three treatment groups (p<0.05). It was observed that the decrease in mean pulse pressure values was statistically significantly lower in patients receiving lercanidipine treatment compared to those receiving benidipine treatment. When the lercanidipine and amlodipine groups were compared, the decrease in the mean pulse pressure values observed in both groups was observed to be higher in patients receiving lercanidipine treatment, although it was close to those in those receiving amlodipine treatment, without any statistical difference.

Systolic blood pressure: The distribution of the decrease in systolic blood pressure who received treatment was shown in Fig. 2. In all groups statistically significant difference was

Table 2: Pulse pressure values of patients

SBP	Amlodipine	Benidipine	Lercanidipine	p-value
Before	56.1±14.0	57.1±14.8	56.9±14.5	0.62
After	47.2±9.0^	50.1±10.7	46.3±8.9*	<0.001
p-value	<0.01	<0.01	<0.01	
Δ	-8.9	-7.0	-10.6	

SBP: Systolic blood pressure, ^p<0.05 vs Benidipine and *p<0.05 vs Benidipine

Table 3: Blood pressure values of patients

SBP	Amlodipine	Benidipine	Lercanidipine	p-value
Before	143.6±15.8	144.1±10.1	145.1±16.9	0.31
After	128.2±14.1	131.8±13.9	127.3±15.2^	0.01
Δ	-15.4	-12.3±15.1	-17.8±16.5	
p-value	<0.001	<0.001	<0.001	
DBP				
Before	87.6±8.2	87.0±9.0	88.2±5.8	0.60
After	81.0±7.9	81.7±8.9	81.0±6.7	0.49
Δ	-6.6	-5.3	-7.2	
p	<0.01	<0.01	<0.01	

SBP: Systolic blood pressure and ^p< 0.05 vs benidipine and amlodipine

Table 4: Rate of blood pressure control

Amlodipine	Benidipine	Lercanidipine	p-value
84.1%	69.1%	89.4%*^^	<0.001

*p<0.05 vs Benidipine and ^^p<0.05 vs Amlodipine

observed between the three treatment groups in terms of the average decrease in systolic blood pressure values (p<0.05). As a result of the Bonferroni Test performed to determine which treatment groups caused this significant difference, it was determined that this difference was caused by benidipine and lercanidipine treatments.

When the changes in blood pressure of the patients before and after treatment were examined, the decrease in mean blood pressure values after treatment was observed to be higher in patients receiving lercanidipine treatment, although it was close to those receiving amlodipine treatment, without any statistical difference. The decrease in mean blood pressure values in patients receiving lercanidipine treatment was observed to be statistically significantly higher in the lercanidipine group compared to those receiving benidipine treatment (p<0.05) (Fig. 2).

At the end of the follow-up, (Table 2) bPP was decreased by each DH-CCB, compared with baseline values (p<0.01). However, the comparison between groups shows a statistically significant difference (p<0.001) because bPP was decreased by 8.9 mm Hg with amlodipine, 7.0 mm Hg with benidipine and 10.6 mm Hg with lercanidipine. The difference between benidipine and both amlodipine and lercanidipine was statistically significant (p<0.05), while no significant difference was obtained between amlodipine and lercanidipine.

Systolic/diastolic BP (Table 3) was significantly lowered in the three patient groups (p<0.001). Particularly it was reduced by 15.4/6.6 mm Hg with amlodipine, 12.3/5.3 mm Hg with benidipine and by 17.8/7.2 mm Hg with lercanidipine. However, amlodipine and benidipine, lowered less than lercanidipine SBP (p<0.05), while there was no significant difference on DBP (p = 0.49).

Blood pressure control: The BP was controlled in 84.1, 69.1 and 89.4% of patients assigned to amlodipine, benidipine and lercanidipine respectively (Table 4). The rate obtained with lercanidipine resulted significantly higher compared with benidipine and amlodipine (p<0.05). No statistical difference was observed between the patient groups receiving amlodipine and lercanidipine treatment. A statistically significant proportion of patients reaching the lowest target blood pressure values was observed in the patient group receiving benidipine treatment (p<0.001).

Adverse events: No clinically significant adverse events were reported by patients or observed by the physicians.

DISCUSSION

Hypertension and pulse pressure, which are independent risk factors for cardiovascular disease and associated with arterial stiffness in elderly patients, are important in assessing cardiovascular system health[1,2]. Pulse pressure has implications for both cardiovascular diseases as well as many non-cardiovascular diseases. Pulse pressure naturally increases over time as individuals' age due to arteriosclerosis and diffuse vascular stiffening[14]. The assessment of arterial stiffness with

most, non-invasive, accurate methods, is not easy in routine clinical practice and it is not recommended by different guidelines[15-18], therefore brachial PP, evaluated as SBP-DBP, has been suggested as a valid tool to assess arterial stiffness[7,19-23]. Moreover, there is no significant difference between central and brachial BP in the ability to predict CV outcome[8,16]. Pulse pressure has implications for both cardiovascular diseases as well as many non-cardiovascular diseases. A vast amount of diagnostic, prognostic and prophylactic value can be derived from the proper monitoring and interpretation of pulse pressure. In this study, as a subgroup analysis of the large HYT study[13] conducted in hypertensive patients treated with amlodipine, benidipine and lercanidipine monotherapy for 6 months, the effect of amlodipine, benidipine and lercanidipine monotherapy on pulse pressure measured by the difference between systolic and diastolic blood pressure was investigated. The data of primary measured parameters show a significant reduction of bPP, with different intensities between the three treatment groups ($p<0.05$). The lercanidipine group was the group that provided the highest decrease in pulse pressure. The reduction of bPP obtained with lercanidipine (-10.6 mm Hg) is almost similar to -12 mm Hg previously reported in patients with isolated systolic hypertension[24]. Also consistent with the results of this study, reports from 3 open studies in patients at least 60 years old show that lercanidipine provides significant reductions in systolic, diastolic and pulse pressure in this patient population[25-27]. In addition to these benidipine lowered less than amlodipine (- 7.0 vs -8.9 mm Hg, $p<0.05$) and lercanidipine (- 7.0 vs -10.6 mm Hg, $p<0.05$) bPP. Therefore, in this study, benidipine had a lower effect than amlodipine and lercanidipine in improving the hemodynamic aspect of arterial stiffness. This result is in agreement with previous trials, that reported -6.1/-6.3 or +1 mm Hg changes on bPP with benidipine[28-30].

When comparing the decrease in blood pressure between groups, amlodipine, benidipine and lercanidipine significantly lowered SBP ($p<0.001$) and DBP ($p<0.05$), compared with baseline, but the effect of lercanidipine was significantly greater ($p<0.05$) than that of amlodipine and benidipine on SBP. There are many studies in the literature showing that lercanidipine is effective in lowering blood pressure, consistent with the results of our study. In a double-blind, placebo-controlled study of 144 elderly patients with hypertension (aged 60-85 years), lercanidipine 10 mg/day for 4 weeks reduced systolic and diastolic blood pressure to a greater extent than placebo (15 vs 7 mm Hg and 10 vs 6 mm Hg, respectively, $p<0.01$ for diastolic blood pressure) and increased the response rate (59 vs 38%, $p<0.05$)[31]. In an open study of 756 patients, lercanidipine (10-20 mg/day for 8 weeks) reduced blood pressure to a similar extent in patients under and over 65 years. Amlodipine shows a variable effect on bPP (+0.1, -4.6, +0.4 mm Hg) in subjects with essential hypertension[14,32,33], however, the reduction obtained in our study (-8.9 mm Hg) is higher than these data. Blood pressure control (PB<140/90) was achieved in a large proportion of patients treated with lercanidipine (89.4%) and amlodipine (84.1%) than with benidipine (69.1%), with a statistically significant difference ($p<0.05$) between lercanidipine, amlodipine and benidipine.

CONCLUSION

The results showed that amlodipine and lercanidipine, differently from benidipine, improve more bPP, a marker of arterial stiffness. Even if the difference between amlodipine and lercanidipine was not significantly different, lercanidipine decreased more than amlodipine bPP. In addition, benidipine decreased less than amlodipine and lercanidipine SBP. This finding explains the differences observed on bPP. The rate of patients with BP<140/90 mm Hg was higher with amlodipine and lercanidipine, than with benidipine. Globally these data suggested a low potential cardioprotective effects of benidipine, being bPP and BP correlate with the risk of cardiovascular outcome in hypertensive patients.

SIGNIFICANCE STATEMENT

The PP associated with high blood pressure is an important treatment target because it directly affects cardiac outcomes and organ damage. Dihydropyridine calcium blockers and renin-angiotensin-aldosterone inhibitors are used in the treatment of brachial and central PP. The aim of this study was to compare pulse pressure, blood pressure, blood pressure control values of hypertension patients treated with amlodipine, benidipine and lercanidipine. This study is original and important as there is no study comparing lercanidipine with other calcium channel blockers in Turkey. At the end of the follow-up, bPP was decreased by 8.9 mm Hg with amlodipine, 7.0 mm Hg with benidipine and 10.6 mm Hg with lercanidipine. Current results suggested a lesser potential cardioprotective effect of benidipine, compared with amlodipine and lercanidipine.

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