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Original Article

Pharmacology Section

An Open Label Parallel Group Study to Assess the Effects of Amlodipine and Cilnidipine on Pulse Wave Velocity and Augmentation Pressures in Mild to Moderate Essential Hypertensive Patients

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ABSTRACT

Introduction: Hypertension is a major cardiovascular risk factor, which affects both large and small arteries. Because of the associated morbidity and mortality and the cost to society, it is an important public health challenge. Population based studies have reported that large artery stiffness is an important determinant of cardiovascular events and mortality in general population and in patients with hypertension. This study was designed to compare the effects of 8 weeks blood pressure control using Amlodepine and cilnidipine on haemodynamic parameters and vascular indices in mild to moderate hypertensive patients.

Materials and Methods: A total of 60 patients were enrolled in the study. Thirty patients were randomly allocated to either Amlodipine 5 mg OD or Cilnidipine 10 mg OD for duration of eight weeks. Blood Pressure (BP), Heart Rate (HR), carotid-femoral Pulse Wave Velocity (cf PWV), Augmentation Index (AIx) and Aortic augmentation pressure (AoAP) were measured at baseline and at the end of eight weeks.

Results: The mean change in the central artery stiffness from baseline to week-8 in the Amlodipine group as compared to Cilnidipine group cf PWV -139.3±27.7 vs. -234.1±74.8 cm/s p=<0.0001, AoAP -3.8±1.5 vs. -5.6±3.3 mm of Hg p=0.008 and AIx -6.8±2.4 vs. -10.8±4.4%, p=<0.0001 respectively.

Conclusion: This study showed that the L/N-type calcium channel antagonist Cilnidipine has a similar antihypertensive action to Amlodipine, but is superior in improving the arterial stiffness.

Keywords: Arterial stiffness, Augmentation Index, Carotid-femoral pulse wave velocity

INTRODUCTION

Hypertension is one of the most common disease afflicting humans throughout the world. Because of the associated morbidity and mortality and the cost to society, it is an important public health challenge as well [1].

The associated cardiovascular risk factors with hypertension syndrome [2] are obesity, accelerated atherogenicity, left ventricular hypertrophy and dysfunction, changes in blood clotting mechanisms, changes in renal function, abnormalities in neurohormonal functions, abnormal insulin and glucose metabolism, endothelial dysfunction and decreased arterial compliance (increased arterial stiffness).

Increase in arterial stiffness may results in higher systolic blood pressure (SBP); lower diastolic blood pressure (DBP) and wide pulse pressure (PP) all conferring greater cardiovascular and total mortality risk. Increased arterial stiffness through an elevation of SBP enhances the left ventricular load and favours cardiac hypertrophy and, through reduction of DBP, results in a decrease in the perfusion pressure of the coronary arteries, thus contributing to myocardial ischemia. The degree of arterial stiffness, obtained in various populations, has been found to be a powerful independent marker of vascular target organ damage and an independent prognostic predictor for cardiovascular morbidity, as well as cardiovascular and all cause mortality [2-7]. Measuring pulse wave velocity (PWV) to assess arterial stiffness is a simple and reproducible method. The underlying principles and technique of this method have been described in detail previously. Several experimental studies have shown that PWV is related to the arterial wall structure, function, geometry and endothelium functions [8]. Amlodipine and Cilnidipine both were calcium channel blockers with greater effect in reducing blood pressure (BP) and decrease intraglomerular pressure by dilating the efferent arterioles [9,10].

This study was designed to compare the effects of 8 weeks blood pressure (BP) control using Amlodepine and cilnidipine on haemodynamic parameters and vascular indices in mild to moderate hypertensive patients.

The aortic PWV is the “gold standard” marker for measuring arterial stiffness, and is widely used to estimate vascular stiffness and “vascular health” [11]. Dihydropyridine (DHP) calcium channel blockers (CCBs) like Amlodipine are frequently used in the treatment of hypertension, stable angina pectoris and cerebrovascular disease by blocking L-type voltage-gated Ca^{2+} channels. Cilnidipine is a unique Ca^{2+} channel blocker used for hypertensive patients, which inhibits sympathetic N-type Ca^{2+} channels in addition to vascular L-type Ca^{2+} channels [12].

MATERIALS AND METHODS

The Institutional Ethical Committee approved this open label randomized parallel group study protocol conducted during period 2012-2013. Informed consent was obtained from study participants. All the participants who were receiving Amlodepine in the age group between 20 to 60 years with sitting systolic blood pressure between 140-160 mm Hg and diastolic blood pressure between 90-100 Hg. Patients were excluded, if the hypertension was secondary to hepatic, renal, cardiac or endocrine disorders, pregnant or lactating. In the present study, 84 patients were screened and after meeting the inclusion and exclusion criteria, a

total of 60 patients were enrolled in the study. Thirty patients received either Amlodipine 5 mg OD or Cilnidipine 10 mg OD for duration of eight weeks. Blood Pressure (BP), Heart Rate (HR), carotid-femoral Pulse Wave Velocity (cf PWV), Augmentation Index (AIx) and Aortic augmentation pressure (AoAP) were measured at baseline and at the end of eight weeks. Demographic, clinical and laboratory records of the enrolled patients were also recorded. After the completion of the study, the patients were instructed to consult their physician for further management; however, none of the patients were deprived of antihypertensive medication.

PULSE WAVE VELOCITY

The Carotid Femoral (CF) PWV was measured using a Volume-plethysmographic apparatus. (Periscope, M/s Genesis Medical Systems, Hyderabad India). This instrument also records blood pressure and electrocardiogram. The subjects were examined in the spine position after a 10 minutes rest, with electrodes connected to all the four limbs and cuffs wrapped on both the brachia and ankles. The plethysmographic sensor and the oscillometric pressure sensors positioned in these cuffs records volume waveforms and blood pressure respectively. Initially the brachial ankle pulse wave velocities (baPWV) of the right and left were obtained from the stored wave forms. Subsequently, cf PWV was calculated automatically from the mathematical equation. cf PWV= 0.833* average baPWV-233.3 [13-15]. Augmentation index (AIx) was calculated as the increment in pressure from the first shoulder in the ascending aortic pressure wave to the peak of this wave, expressed as a percentage of the peak ascending aortic pressure wave. AIx=100*ΔP/PP. where ΔP is Augmentation pressure [16].

STATISTICAL ANALYSIS

The statistical analysis was carried using Graph pad prism software (Version-5, USA) continuous data was presented as Mean±SD and Categorical as actual numbers and percentages. For normally distributed data, with-in group analysis was performed by using paired t-test and between group analyses by unpaired t-test. Non-normally distributed data was analysed by using non-parametric "Mann-Whitney U test". Categorical variables were analysed with "Fischer's exact test". All the efficacy parameters were presented as absolute change from baseline. A negative sign indicates decrease and vice versa. For statistical significance, a two tailed probability value of less than 0.05 was considered. A sample of 25 patients per group was required to demonstrate an estimated change in primary efficacy variable cf PWV of 1 m/s from baseline in both groups, with 80% power to detect the difference and two sided alpha error of 0.05 [17]. Additionally 5 patients were added to pay off for drop outs.

Parameters	Amlodipine N=30	Cilnidipine N=30	
Demographic	**Mean ±SD**	**Mean ±SD**	**p-value**
Age(years)	50.7±6.8	49.9±8.9	0.72
Gender(M/F)	21/9	24/6	0.55
Weight (kg)	67.03±14.2	65.27±13.7	0.62
Height(cm)	162.4±10.1	158.77±11.1	0.19
BMI(kg/m^2)	25.3±4.2	25.9±4.7	0.63
Diabetes	12(40%)	10(33.3%)	0.79
Smoking	8(26.7%)	7(23.3%)	1.00
Alcohol	5(16.6%)	4(13.3%)	1.00
Statins	13(43.3%)	9(30%)	0.42
Antiplatelets	6(20%)	8(26.7%)	0.76
Peripheral Haemodynamic			
SBP(mm Hg)	152.4±6.7	149.2±7.0	0.07
DBP(mm Hg)	81.6±8.8	81.5±10.6	0.99
PP(mm Hg)	70.8± 8.8	67.6 ±11.7	0.23
HR(bpm)	82.3±15.5	81.9±11.0	0.89
Central Haemodynamic			
Aortic SBP(mm Hg)	123.8±14.6	125.8±14.7	0.60
Aortic DBP(mm Hg)	78.1±10.6	81.7±10.5	0.20
Aortic PP(mm Hg)	45.6 ±12.3	44.1± 10.9	0.60
Vascular Indices			
AoAP(mm Hg)	11.5±5.4	12.1±6.4	0.72
AoAIx	24.6±6.2	25.6±10.0	0.65
Cf PWV(cm/sec)	1123.9±167	1113.6±263	0.86

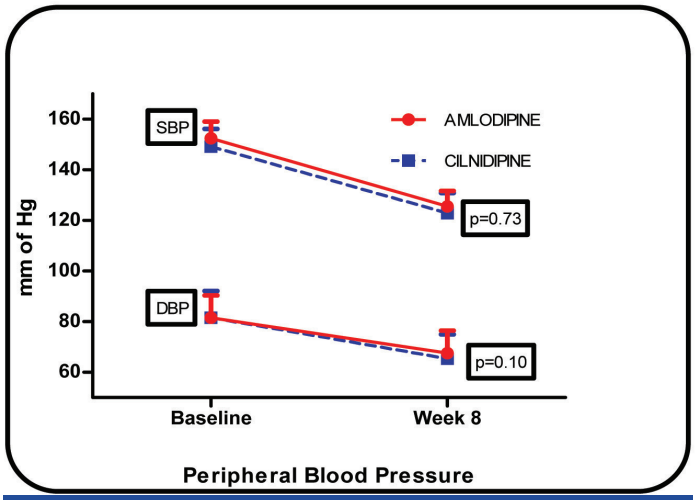
[Table/Fig-1]: Baseline demographic, haemodynamic and vascular indices of mild-moderate essential hypertensive patients according to treatment group.
SBP-Systolic Blood Pressure, MBP-Mean Blood Pressure, DBP-Diastolic Blood Pressure, PP—Pulse Pressure, HR-Heart Rate, AoAP-Aortic Augmentation pressure, AoAIx- Aortic Augmentation Index, cf PWV- Carotid femoral Pulse Wave Velocity

RESULTS

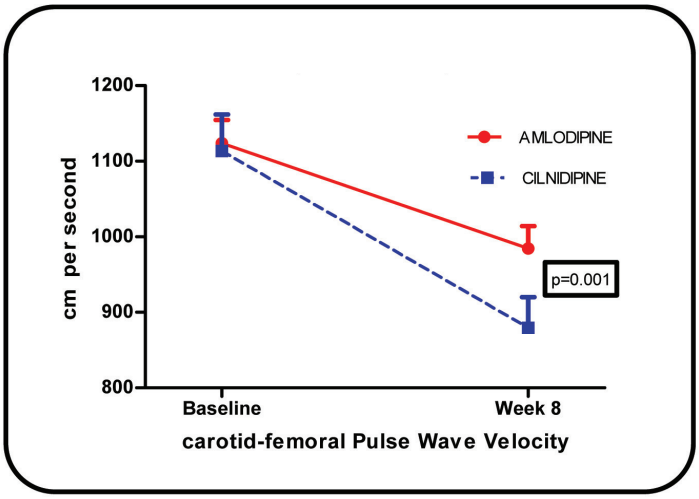
In the present comparative study, there were 21 males and 9 females in the Amlodipine group and 24 males and 6 females in the Cilnidipine group. There was no statistically significant difference in demographic, anthropometric and clinical characteristics of Amlodipine and Cilnidipine groups. Additionally, baseline haemodynamic and vascular indices parameters were also similar between the two groups as shown in [Table/Fig-1]. After eight weeks of treatment with Amlodipine and Cilnidipine, it was found that [Table/Fig-2] there was a significant change in the haemodynamic and vascular indices from baseline in each group. [Table/Fig-3-6]. When we evaluated the absolute change from baseline to eight weeks in the peripheral haemodynamic parameters between Amlodipine and Cilnidipine groups [Table/Fig-7], it became apparent that there

Parameters	AMLODIPINE N=30		p-value	CILNIDIPINE N=30		p-value
Peripheral Haemodynamic	**Baseline**	**Week 8**		**Baseline**	**Week 8**	
SBP(mm Hg)	152.4±6.7	125.5±6.1	<0.0001	149.2±7.0	122.8±8.0	<0.0001
DBP(mm Hg)	81.6±8.8	67.6±8.8	<0.0001	81.5±10.6	65.3±9.7	<0.0001
PP(mm Hg)	70.8± 8.8	57.9± 8.1	<0.0001	67.6 ±11.7	57.5 ±9.3	<0.0001
HR(bpm)	82.3±15.5	84.2±11.9	0.24	81.9±11.0	80.6±10.2	0.23
Central Haemodynamic						
Aortic SBP(mm Hg)	123.8±14.6	114.8±14	<0.0001	125.8±14	112.1±13	<0.0001
Aortic DBP(mm Hg)	78.1±10.6	73.5±9.4	0.02	81.7±10.5	70.3±13.1	<0.0001
Aortic PP(mm Hg)	45.6 ±12.3	41.4 ±14.9	0.02	44.1± 10.9	41.8 ±10.9	0.22
Vascular Indices						
AoAP(mm Hg)	11.5±5.4	7.7±4.8	<0.0001	12.1±6.4	6.5±4.1	<0.0001
AoAIx	24.6±6.2	17.8±5.4	<0.0001	25.6±10.0	14.9±7.8	<0.0001
Cf PWV(cm/sec)	1124±167	984±162	<0.0001	1113±263	879±223	<0.0001

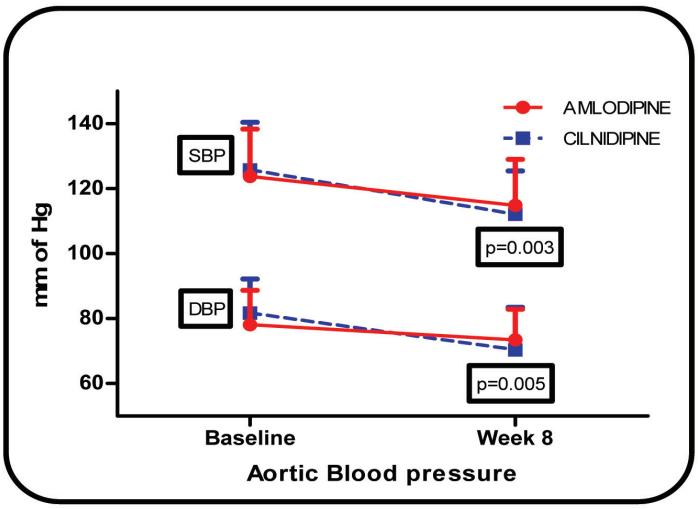
[Table/Fig-2]: Comparison of haemodynamic and vascular indices before and after Amlodipine and Cilnidipine treatment
SBP-Systolic Blood Pressure, MBP-Mean Blood Pressure, DBP-Diastolic Blood Pressure, PP—Pulse Pressure, HR-Heart Rate, AoAP-Aortic Augmentation pressure, AoAIx-Aortic Augmentation Index ,cf PWV- Carotid femoral Pulse Wave Velocity



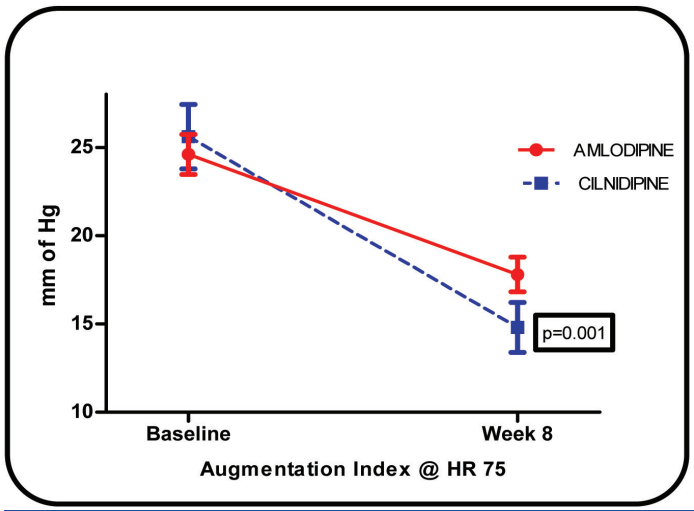
[Table/Fig-3]: Showing comparison of Systemic blood pressure before and after Amlodipine and Cilnidipine treatment



[Table/Fig-5]: Showing comparison of cf-PWV before and after Amlodipine and Cilnidipine treatment



[Table/Fig-4]: Showing comparison of aortic blood pressure before and after Amlodipine and Cilnidipine treatment



[Table/Fig-6]: Showing comparison of AIx @ HR 75 before and after Amlodipine and Cilnidipine treatment

was no statistically significant difference between the two groups. However, we found a statistically significant change in the central haemodynamic and vascular indices in the Cilnidipine group as compared to Amlodipine. All the subjects who participated in the study showed good compliance and none of them developed side effects.

DISCUSSION

Hypertension is a major cardiovascular risk factor, which affects both large and small arteries. Population based studies have reported that large artery stiffness is an important determinant of cardiovascular events and mortality in general population and in patients with hypertension [9]. Calcium channel blockers (CCB) are frequently used drugs to treat hypertensive patients in our hospital setup. The mechanism of action in hypertension is due to its inhibition of calcium influx into vascular smooth muscle cells (VMC) that causes relaxation of VMC, decreased after load and systemic blood pressure. It is also evident from the reports that dihydropyridine calcium antagonists improve arterial wall stiffness [18,19].

We studied the haemodynamic and vascular effects of Amlodipine and Cilnidipine and found that there was a statistically significant decrease in peripheral blood pressure when compared to baseline in both the groups after eight weeks but not in Heart rate. Satoshi Morimoto et al., also reported that Amlodipine at 5 mg daily dosage and Cilnidipine at a daily dose of 10 mg per day are equally effective in reducing the blood pressure in patients with mild to moderate hypertension [20]. Additionally, they also improved central blood pressure as well as indices of arterial stiffness (cf PWV &AIx). On comparison between the medications; the decrease in peripheral blood pressure between two groups was not statistically significant. For a similar reduction in peripheral blood pressures, we observed that Cilnidipine showed significantly higher improvement in aortic blood pressure and AoAP as well as markers of arterial stiffness (cf-PWV & AIx) than with Amlodipine.

Mean Change in Parameters	Amlodipine	Cilnidipine	p-value
Peripheral Haemodynamic	Baseline	Week 8	
ΔSBP(mm Hg)	-26.9±4.9	-26.3±7.6	0.73
ΔDBP(mm Hg)	-14.0±3.6	-16.2±6.3	0.10
ΔPP(mm Hg)	-4.6± 5.4	-5± 8.2	0.82
ΔHR(bpm)	1.8±8.4	-1.3±5.8	0.10
Central Haemodynamic			
ΔAortic SBP(mm Hg)	-8.9±2.3	-13.7±8.1	0.003
ΔAortic DBP(mm Hg)	-4.6±10.3	-11.4±7.2	0.005
Aortic PP(mm Hg)	-4.29± 9.6	-2.26± 9.8	0.42
Vascular Indices			
ΔAoAP(mm Hg)	-3.8±1.5	-5.6±3.3	0.008
ΔAoAIx	-6.8±2.4	-10.8±4.4	0.001
Δcf-PWV(cm/sec)	-139.3±27.7	-234.1±74.8	0.001

[Table/Fig-7]: Comparison Of mean change from baseline in the haemodynamic& vascular indices between Amlodipine and Cilnidipine Groups.
SBP-Systolic Blood Pressure, MBP-Mean Blood Pressure, DBP-Diastolic Blood Pressure, PP—Pulse Pressure, HR-Heart Rate, AoAP-Aortic Augmentation pressure, AoAIx- Aortic Augmentation Index ,cf PWV- Carotid femoral Pulse Wave Velocity

The proposed mechanisms for such an improvement in cf PWV and AIx by CCBs are acute changes in the functional properties such as vascular smooth muscle relaxation, reduction in wave reflections, improvement in endothelial dysfunction or regulation of sympathetic nervous system. It is unlikely that the structural changes would occur after 8 weeks of therapy, the likely mechanism for the improvement in arterial compliance in present study may be due to improved vascular smooth muscle relaxation possibly by increased bioavailability of NO.

Studies have reported that CCBs also have an anti-inflammatory and anti-oxidative effect independent of their effect on lowering BP [21]. Amlodipine has been reported to increase endothelial nitric oxide synthase (eNOS) activity [22] and to improve endothelial functions [23] in experimental models. Hok Sum Leung et al., showed that Cilnidipine also increases release or bioavailability of NO, due to elevated endothelial Ca^{2+} ions in arteries [24]. Chandra et al., in his study confirmed Cilnidipine significantly induced eNOS activity, as well as increased eNOS concentration in rats when compared with Amlodipine. Also, Cilnidipine is both an L/N-type CCB, has an inhibitory effect on cardiovascular sympathetic neurotransmission in contrast to L type CCB like Amlodipine [25]. One or all of such mechanisms could be the possible explanations for such an improvement over Amlodipine. This makes it useful in the treatment of cardiovascular diseases associated with diminished NO release, such as atherosclerosis. Moreover, this mechanism is independent of its effect on L/N-type receptors [26].

STUDY LIMITATIONS

In the present study, we have used non-invasive method, which simultaneously records blood pressure, pressure waves and also calculates the parameters of velocity at different points from these recordings. Although the present equipment data is well validated, however, the accuracy cannot be comparable to the invasive haemodynamic monitoring. Due to ethical reasons, invasive monitoring was not attempted. Cilnidipine showed a better improvement in arterial stiffness than Amlodipine without much difference in blood pressure reduction. However, such an interpretation needs carefulness because the time at which they took the medication before each study day, concomitant medications, co-morbid conditions and wider confidence intervals in electrophysiological parameters could have been confounding factors. Larger-scale studies are required to confirm above stated results.

CONCLUSION

This study showed that the L/N-type calcium channel antagonist cilnidipine has a similar antihypertensive action to the L-type calcium channel antagonist amlodipine, but is superior in terms of improving arterial stiffness and central aortic pressures. Cilnidipine can be recommended as the treatment of choice for patients with essential hypertension. However Larger-scale studies are required to confirm above stated results.

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