

ORIGINAL ARTICLE - PHARMACOLOGY

**A Comparative Study On Efficacy And Safety Of Amlodipine And Cilnidipine
In The Treatment Of Mild To Moderate Essential Hypertension.**

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ABSTRACT

BACKGROUND: Calcium channel blockers are one of the first line drugs used in the treatment of newly diagnosed case of primary essential hypertension. Cilnidipine is a new calcium channel blocker which acts on both L and N-type of calcium channel unlike Amlodipine which acts only on L-type calcium channels. Hence this study was done to compare the efficacy and safety of amlodipine and cilnidipine in patients with essential hypertension.

METHODS: 60 patients with newly diagnosed essential hypertension were enrolled for the study. They were randomly assigned to Amlodipine (N=30) and Cilnidipine (N=30) groups. Amlodipine 5mg and Cilnidipine 10 mg was given once daily for a period of 60 days.

RESULT: After 60 days of treatment the mean systolic blood pressure was 120.80 ± 1.45 and 120 mmHg ($p=0.004$). and the mean diastolic pressure was 80.33 ± 0.92 and 80 mmHg ($p=0.052$) respectively for Amlodipine and Cilnidipine group. There was a reduction in heart rate for patients treated with cilnidipine. In the second visit 7(23%) patient treated with amlodipine presented with ankle edema which was highly significant ($p=0.014$). There was significant reduction in both systolic and diastolic blood pressure in first and second visit for both Amlodipine and Cilnidipine group. Adverse events were less, and tolerability was better with Cilnidipine.

CONCLUSION: Novel calcium channel blocker Cilnidipine with its activity on both L-and N-type calcium channel could be beneficial than Amlodipine that blocks only L-type calcium channel in terms of tolerability and safety.

Keywords: Hypertension; L- and N-type calcium channel blocker; Cilnidipine.

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<https://dx.doi.org/10.31975/NJBMS.2020.10035>

INTRODUCTION:

“Hypertension (HTN) is a chronic medical condition with persistently elevated arterial blood pressure.”¹ It is a growing health issue in south Asia with the second largest risk factor for disability-adjusted life year lost.² Early Detection and effective management of hypertension decreases the risk of stroke, myocardial infarction, chronic kidney disease and heart failure.³

In India hypertension accounts for 57% of all stroke-related deaths and 24% of coronary artery disease-related deaths. Thus, blood pressure reduction can reduce the significant proportion of death and disability.²

Diuretics, α -blockers, β -blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB), and calcium channel blockers (CCBs) are the major classes of drugs used in the treatment of hypertension.⁴ Among these drugs, calcium channel blocker has become the most important initial agents for antihypertensive monotherapy. Among CCBs, dihydropyridines are the one group most frequently prescribed in China and other Eastern Asian countries.⁵

Amlodipine, a third generation dihydropyridine has an outstanding pharmacokinetic and pharmacodynamic profile. Slow absorption, long plasma half-life, and less reflex tachycardia make it the best choice. But the major drawback is ankle edema and almost 9.3% of patients discontinue the treatment.⁶ Cilnidipine is a novel and unique dihydropyridine derivative CCB blocker with potent inhibitory action against both L-type and N-type voltage-dependent calcium channels.⁷ It inhibits sympathomimetic activity in contrast to other dihydropyridines. The incidence of ankle edema is low with cilnidipine when compared to amlodipine.⁸

Comparing the efficacy between Amlodipine and Cilnidipine help in identifying the most effective drug for controlling systolic and diastolic blood pressure among hypertensive patients. The study is designed to compare the efficacy and safety of Amlodipine and Cilnidipine among rural population with essential hypertension in Salem, Tamil Nadu, India.

OBJECTIVES OF THE STUDY:

1. To evaluate the efficacy of Amlodipine and Cilnidipine in controlling the systolic and diastolic blood pressure in patients diagnosed

with mild to moderate essential hypertension.

2. To compare the efficacy between Amlodipine and Cilnidipine in controlling the systolic and diastolic blood pressure in patients diagnosed with mild to moderate essential hypertension.
3. To compare the safety and tolerability of the above drugs in terms of adverse drug monitoring.

MATERIALS AND METHODS:

This is a Single Centre, Prospective, open labelled, Comparative study conducted after receiving approval from the institutional ethical committee of Vinayaka Missions Kirupanandavariyar medical college, Salem. Newly diagnosed cases of hypertension attending the general medicine outpatient department at Vinayaka missions Kirupanandavariyar medical college and hospital, Salem were enrolled after obtaining the informed consent prior to participation. Patient were screened for the study based on the following criteria

INCLUSION CRITERIA:

Patients with systolic blood pressure between 140 to 160 mmHg and diastolic blood pressure of 90 to 100 mmHg⁶ between the age group 30 to 55 years were enrolled in the study.

EXCLUSION CRITERIA:

Secondary hypertension, patients with other comorbidity like renal, cardiac, hepatic and endocrine disorders and pregnant and lactating women was excluded from the study.

Patient enrolled in the study were assured confidentiality. The selected patients were divided into two groups (group A and group B). They were randomly assigned to two groups, a group for Amlodipine and a group for Cilnidipine. It was done in 1:1 ratio as per their registration number. After taking detailed history, physical examination, clinical examination (systolic blood pressure, diastolic blood pressure and heart rate) the laboratory investigations (Hb, TC, DC, ESR, LFT, RFT, ECG) .The patients in group A was given Amlodipine 5mg once daily and patient in group B was given Cilnidipine 10mg once daily half an hour after breakfast for a period of 8 weeks. Patients enrolled in the study were not permitted to use any other medications apart from the antihypertensive drugs given to them. Every patient was seen a total of three times during the study. Visit 0, i.e. baseline visit on the day of recruitment, visit 1 after 30 days of medication and visit 2 after 60 days of treatment. During each visit the systolic blood pressure, diastolic blood

pressure and heart rate were measured. At the end of 8 weeks, clinical and laboratory parameters were repeated. After the study, the patient was instructed to consult their physicians for further management. The efficacy of the drug was assessed by measuring the blood pressure using manual sphygmomanometer. Patient compliance was assessed by pill count method on every visit and adverse drug reactions are noted by periodic phone calls and at every visit.

STATISTICAL ANALYSIS:

Independent two sample t-test was carried out to evaluate the efficacy of amlodipine and cilnidipine. The p value which is probability that the result based on the t- test is computed for hypothesis testing. A p value less than 0.05 were considered statistically significant. Further analysis was carried out using chi-squared test (χ^2).

RESULT:

In this comparative study, 60 patients were recruited (34(57%) male and 26 (43%) female). Patients between the age of 45 and 55 were selected. Mean age of the patient recruited for the study was 48.20±3.74 years and 49.43±5.10 years for Amlodipine and Cilnidipine group respectively. Both the groups were comparable in all other aspects. There were no statistically significant differences in demographic, anthropometric

and clinical characteristics of Amlodipine and Cilnidipine groups. (Table 1)

Table 1: Baseline Demographic data

Parameters	Amlodipine (Mean±SD)	Cilnidipine (Mean±SD)	P value (Mean±SD)
Age(yrs)	48.20 ±3.74	49.43 ±5.10	0.290
Weight(kg)	73.20 ±12.33	75.20 ±12.33	0.532
Height(cm)	167.53 ±8.79	168.07 ±9.02	0.817

Table 2 shows that the mean systolic blood pressure at visit 0 was 142.33±2.93 and 142.20±3.50 mmHg respectively. At visit 1 it reduced to 121.93±2.07 and 120.53±1.17 mmHg (p=0.002) and at visit 2 the mean systolic blood pressure was 120.80±1.45 and 120(p=0.004). Table 3 shows that the mean diastolic blood pressure at visit 0 was 90.80±1.45 and 90.60±1.5 mmHg. At visit 1 it was reduced to 80.53±1.28 and 80(p=0.026) and at visit 2, 80.33±0.92 and 80mmHg (p=0.052) respectively. There was a significant reduction in both systolic and diastolic blood pressure in first and second visit for both Amlodipine and Cilnidipine group. The mean heart rate at visit zero was 74.07±9.13 in Amlodipine group and 70.07±6.25 in Cilnidipine group. At visit 1 there was no reduction in HR. At the end of 2 months of treatment there was a significant reduction in HR 73.60 (±6.27) and 68.87 (±5.27) (p=0.002). Cilnidipine showed better reduction in HR in comparison with Amlodipine(Table4).

Table 2: SBP at Visit 0, Visit 1, Visit 2

	Amlodipine (Mean±SD)	Cilnidipine (Mean±SD)	P Value
Visit 0	142.33±2.93	142.20 ±3.50	0.873
Visit 1	121.93 ±2.07	120.53 ±1.17	0.002**
Visit 2	120.80 ±1.45	120.00 ±0.00	0.004**

*P Value <0.05 is Significant

Table 3: DBP at Visit 0, Visit 1, Visit 2

	Amlodipine (Mean±SD)	Cilnidipine (Mean±SD)	P Value
Visit 0	90.80 ±1.45	90.60 ±1.5	0.601
Visit 1	80.53 ±1.28	80.00 ±0.00	0.026*
Visit 2	80.33 ±0.92	80.00 ±0.00	0.052

Table 4: Heart Rate at Visit 0, Visit 1, Visit 2

	Amlodipine (Mean±SD)	Cilnidipine (Mean±SD)	P Value
Visit 0	74.07 ±9.13	70.07 ±6.25	0.053
Visit 1	74.40 ±6.79	70.07 ±5.72	0.044*
Visit 2	73.60 ±6.27	68.87 ±5.27	0.002**

Table 5: Adverse effects between two groups – One month and two month

Adverse Effect	Drug			
	Amlodipine		Cilnidipine	
	N	%	N	%
At 1 month	19	63	15	50
At 2 months	14	47	2	7

*P Value <0.05 is Significant

At visit 1, 19 patients treated with Amlodipine and 15 patients treated with Cilnidipine had adverse effect, while in the second visit 14 patient treated with Amlodipine and 2 patients treated with Cilnidipine presented with adverse effects as listed in table 5. Table 6 & 7 demonstrates the adverse effects suffered by patients in each group.

Table 6: Details of Adverse Effects in each group after one month

Adverse Effect	Drug				Total		Chi square test	P value
	Amlodipine		Cilnidipine		N	%		
	N	%	N	%				
No ADR	11	37	15	50	26	43	12.39	0.575
Headache	3	10	3	10	6	10		
Fatigue	5	17	4	13	9	15		
Nausea	1	3	2	7	3	5		
Vomiting			1	3	1	2		
Abdominal pain	2	7	1	3	3	5		
Muscle pain	1	3			1	2		
Headache + nausea			1	3	1	2		
Headache + fatigue	2	7			2	3		
Vomiting + abdominal pain	1	3			1	2		
Muscle pain + fatigue	1	3	1	3	2	3		
Headache + abdominal pain	1	3			1	2		
Headache + vomiting	1	3			1	2		
Muscle pain + fatigue + headache	1	3			1	2		
Fatigue + nausea			2	7	2	3		
Total	30	100	30	100	60	100		

Table 7: Details of Adverse Effects in each group after Two months

Adverse Effect	Drug				Total		Chi square test	P value
	Amlodipine		Cilnidipine		N	%		
	N	%	N	%				
No ADR	16	53	28	94	44	73	14.273	0.014*
Headache	3	10	1	3	4	7		
Fatigue	2	7			2	3		
Abdominal pain	1	3	1	3	2	3		
Ankle edema	7	23			7	12		
Headache+ nausea+ muscle pain	1	3			1	2		
Total	30	100	30	100	60	100		

DISCUSSION:

Hypertension is a key concern among patients causing various health related issues. Cardiovascular morbidity and mortality increase as both systolic and diastolic blood pressure rise. The study has analyzed the effect of Amlodipine 5 mg once daily and Cilnidipine 10 mg once daily in hypertensive patients.

Calcium channel blocker is a commonly used drug to treat hypertension in our hospital setup. It inhibits the calcium influx in to vascular smooth muscle cells thereby relaxing them and causes vasodilation and fall in blood pressure¹². Clinical effect of dihydropyridine calcium channel blocker is due to its action on L-type calcium channel predominantly present in arterioles.¹³ Despite with same efficacy in controlling blood pressure, the incidence of pedal edema varies between calcium channel blockers. It can be explained by its difference in influence on peripheral

arteries.¹⁴ The drugs that specifically inhibit L-type calcium channel reduce blood pressure by dilating the resistance arterioles, but not venules. Hence the pressure in the afferent capillaries peripheral to the resistance arteries increases above the oncotic pressure and extravasation occurs. It was noted that when an L- type calcium channel blocker was combined with angiotensin converting enzyme inhibitor the incidence of pedal edema reduced.¹⁵

N-type calcium channels are distributed in the neurons and have a role in regulation of the sympathetic activity.¹⁶ The venules are innervated by sympathetic neurons hence the N-type calcium channel blocker causes venodilation.¹⁷

Cilnidipine is a 1,4-dihydropyridine calcium channel blocker that suppresses the influx of calcium ions via both L and N type calcium channel this leads to vascular smooth muscle relaxation and arterial dilation and reduction in blood pressure.¹⁸ Cilnidipine also block N-type calcium channel in the peripheral sympathetic nerve thereby suppressing catecholamine release.¹⁹ Fan et al reported that Cilnidipine have a unique property of enhancing synthesis of endothelial nitric oxide thereby vasodilation and fall in blood pressure.²⁰ Cilnidipine have

a long duration of action and can be administered once daily.²¹

In a clinical study conducted by Nagahama S et al²² in 2007 and Limura O et al²³ in 1993 the anti-hypertensive effect of cilnidipine was demonstrated. The study done by Hoshide et al reported that there was significant reduction in the heart rate of hypertensive patients treated with Cilnidipine than Amlodipine.²⁴

In this study it was found that there was statistically significant decrease in peripheral blood pressure when compared to baseline in both the group after 8 weeks of treatment. The mean systolic blood pressure decreased by 20.4 and 21.67 mmHg after one month of treatment in amlodipine and cilnidipine group respectively. By the end of 2 month of therapy the mean systolic blood pressure dropped to 21.53 and 22.2 mmHg.

The diastolic blood pressure was dropped by 10.27 and 10.6 mmHg after 30 days of therapy and by the end of 60 days of therapy 10.47 and 10.6 mmHg in amlodipine and cilnidipine group respectively. But there were no statistically significant differences between the two group, which shows both the drugs are equally efficacious.

There was a significant drop in heart rate following therapy with both the drugs. In patients treated with amlodipine, after 60

days of treatment there was no significant fall in heart rate where as in cilnidipine treated group after two-month treatment mean heart rate drop by 1.2 beats per min. Satoshi Morimoto et al., reported that Amlodipine 5mg and Cilnidipine 10 mg is equally effective in controlling blood pressure in patient with mild to moderate essential hypertension.²⁵

Ram Mohan et al. studied on the effect of Amlodipine and Cilnidipine on haemodynamic and vascular indices and reported that both the drug have the same efficacy in controlling the blood pressure but the central hemodynamic and vascular indices like pulse wave velocity, arterial stiffness and central aortic pressure improved with Cilnidipine.²⁶ Ranjan Shetty, Vivek et al. studied the tolerance to Cilnidipine in hypertensive with Amlodipine induced edema. In his study 27 patients with Amlodipine induced pedal edema was switched over to Cilnidipine. In a period of 4 weeks all the 27 patients were free of edema. They also reported that there was no significant change in mean arterial pressure or heart rate which means both Amlodipine and cilnidipine was equally efficacious.²⁷

A study by Xu GL, Hui X et al. have shown that cilnidipine is well tolerated by hypertensive patients with very minimal

adverse event such as headache, dizziness, cough and gastrointestinal disturbances which are comparable to amlodipine.²⁸ Hence calcium channel blockers with action on N- type calcium channel can cause dilation of venules through sympathetic system and can reduce the incidence of pedal edema compared to calcium channel blockers that acts only on L-type calcium channels. These findings shared similar results to my study.

Cilnidipine was extensively studied by researchers in its preclinical and clinical developmental stages and is still been studied. It has been proven to have a reno, neuro and cardio protective effect-decrease in heart rate, apart from its BP lowering effect.

Uneyama et al demonstrated that submicro molecular concentration of cilnidipine can effectively suppress N- type calcium channel in isolated sympathetic neurons.²⁹ Nagai H and et al demonstrated the cardioprotective effect of cilnidipine in a rabbit model of myocardial infarction. He reported that cilnidipine decreased the myocardial interstitial norepinephrine level during ischemia and reperfusion period that lead to the reduction of infarct size and the ventricular premature beats.³⁰ Incidence of morning hypertension and White- coat

hypertension was closely associated with sympathetic activity, Cilnidipine have been clinically demonstrated to be effective in such cases.³¹

Kojima s et al³² and Tsuchihashi T et al³³ studied the Reno protective effect of cilnidipine and found outstanding results. They reported Cilnidipine had better Reno protective effect when compared to pure L- type calcium channel blockers. It reduces glomerular filtration pressure, suppresses renin angiotensin aldosterone secretion and reduces the incidence of proteinuria.

The beneficial effect of calcium channel blocker in lipid and carbohydrate metabolism in patients with concurrent type II diabetes mellitus and hypertension have been demonstrated by Takashi et al.³⁴

CONCLUSION:

The calcium channel blocker Amlodipine and Cilnidipine have equal efficacy in reducing the systolic and diastolic blood pressure in patients with mild to moderate essential hypertension. Cilnidipine is a promising fourth generation calcium channel blocker with an outstanding pharmacological profile. Apart from its BP lowering effect Cilnidipine have marked its safety profile and additional benefits on Reno, cardio and neuro protective effects. Cilnidipine being both L and N type calcium

channel blocker it has an additional action on venules there by prevents the incidence of pedal edema, which is not seen in Amlodipine which only acts on L-type calcium channels. Cilnidipine being dual blocker in both L and N type calcium channel does not exhibit reflex tachycardia.

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Received On: 15/2/2020 Revised on: 4/03/2020 Accepted on: 19/03/2020