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Original Research Article

Cilnidipine versus Amlodipine Effectiveness and Tolerability in Patients with Recently Diagnosed Essential Hypertension: A Comparative Analysis

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Abstract

Background: It is suggested that calcium channel blockers (CCBs) will be crucial in managing and controlling hypertension. Calcium channel blockers (CCBs) of the dihydropyridine family, like amlodipine, are extensively utilised due to their potent antihypertensive benefits and lack of significant side effects. However, among the patients, it is frequently linked to the cause of pedal edoema. A novel calcium channel blocker of a new generation called cilnidipine is thought to have fewer adverse effects, lessen pedal edoema, and provide clinically adequate management of hypertension. This research compared the clinical efficacy and tolerability profiles of Amlodipine with Cilnidipine.

Methods: At Nalanda Medical College and Hospital, Patna, Bihar conducted this prospective, double-blind, parallel group study from December 2021 to November 2022. 50 patients were randomly divided into two groups of 25 each based on inclusion and exclusion criteria. Cilendipine 10 mg was given to one group, whereas amlodipine 5 mg tablets were given to the other, both once daily for a period of 12 weeks. There were follow-ups at 2, 4, 8, and 12 weeks. Sitting still, blood pressure readings for both the systolic and diastolic were taken. At 4, 8, and 16 weeks, the dose was adjusted if the patient did not reach the goal blood pressure of 140/90 mmHg. By asking about adverse drug reactions during the follow-up visit and abnormalities in standard laboratory test results at the conclusion, tolerability was evaluated. For analysis, the Z test was utilised.

Results: No statistically significant difference existed between the antihypertensive efficacies of the two medications. In comparison to amlodipine, the number of patients who experienced side effects was much lower in the cilnidipine group. Although the group on cilnidipine saw fewer unfavourable vasodilator reactions, the only other notable difference was the incidence of pedal edoema. This variation in edoema incidence cannot be attributed to the degree of blood pressure lowering.

Conclusion: Comparable in antihypertensive efficacy to amlodipine, cilnidipine is linked to a significantly decreased incidence of vasodilation-related adverse effects, particularly pedal edoema. This superior tolerability profile may improve treatment outcomes by encouraging better medication therapy adherence.

Keywords: Amlodipine, Ankle edema, Cilnidipine, Newly diagnosed essential hypertension.

Introduction

Around 1 billion people worldwide suffer from hypertension. According to estimates, systemic hypertension affects about 30% of India's population.[1] Additionally, hypertension is a significant risk factor for cardiovascular, neurological, renal, and peripheral vascular problems. It is frequently linked to diabetes mellitus, obesity, inactivity, excessive salt intake, and smoking.[2]

Calcium channel blockers (CCBs) are suggested to be a key component of the therapeutic arsenal of antihypertensive medications for the management and control of hypertension. Calcium channel blockers (CCBs) of the dihydropyridine class are widely utilised due to their potent blood pressure-lowering abilities and lack of serious side effects. Amlodipine has historically been the preferred CCB due to its favourable pharmacokinetic and pharmacodynamic profile.[3]

With an average incidence rate of 15% (1.7% to 32%), pedal edoema is one of the most unsettling side effects of amlodipine.[4] The N-type channel is one of the several calcium channel subtypes, and it is thought to have a role in the activation of RAS and subsequent release of catecholamines (Nor-epinephrine). Dual N and L-type calcium channel blockers are becoming more popular because it has been shown that using them reduces the risk of developing RAS.[5]

A third-generation mixed L/N-type CCB called cilnidipine is authorised to treat essential hypertension.6 Additionally, it has been suggested to offer a profile of action that goes beyond the antihypertensive impact, such as reducing the frequency of undesirable side effects such ankle edema.

In order to examine the effectiveness and tolerability of Tab. Cilnidipine 10 mg with Tab. Amlodipine 5 mg in patients with documented essential hypertension, this study was done.

Material and Methods

This was a prospective, randomized, double blind, parallel group study carried out at Nalanda Medical College and Hospital, Patna, Bihar from December 2021 to November 2022. Patients collected from OPD Medicine Department of NMCH, Patna, Bihar.

After acquiring informed written agreement, newly diagnosed patients with mild to moderate essential hypertension (systolic blood pressure between 140 and 179 mmHg and diastolic blood pressure between 90 and 109 mmHg) of both sexes and older than 35 years were enrolled in this study. Patients taking other anti-hypertensive medications, secondary hypertension, obstructive biliary disease, cholestasis or hepatic impairment, renal impairment, aortic stenosis, unstable angina, uncontrolled heart failure, and MI within one month of the attack, pregnant women, nursing mothers, and female patients of childbearing age who weren't using medically prescribed contraceptives were among those who were excluded from the study.

Out of 100 OPD patients who were screened, 50 were enrolled in the study and randomly divided into two groups of 25 patients each. By using separate investigators for each stage of random number generation, enrollment, and patient assignment to treatment groups, simple randomization was carried out and allocation was concealed. Patients in the first group received a pill of cilnidipine 10 mg, while those in the second group initially

received a tablet of amlodipine 5 mg, both once daily for a period of 12 weeks. There were follow-ups at 2, 4, 8, and 12 weeks. Patients underwent a clinical examination and had their medical histories recorded at each visit. Every patient recommended making lifestyle changes. At each visit, the heart rate was documented, and the blood pressure (BP) was measured using the auscultation method with a mercury sphygmomanometer while the patient was sitting after 10 minutes of rest. Before having their blood pressure measured, the patients were asked not to smoke or drink coffee within 30 minutes. Serum creatinine, SGOT, SGPT, and random blood sugar levels were measured in the laboratory on the first day and 12 weeks into the trial.

The decrease in systolic and diastolic blood pressure at baseline served as the main efficacy metric. At the fourth and eighth weeks, the doses of cilnidipine and amlodipine, respectively, were increased by 5 mg and 2.5 mg, respectively, if the patient's target blood pressure of 140/90 mmHg was not reached. Patients who did not reach the desired blood pressure level by the conclusion of the research were classified as non-responders and sent to a doctor for additional care. The existence or absence of adverse medication reactions and changes in laboratory markers were used to evaluate tolerability and safety. Foot edoema, headache, dizziness, flushing, palpitations, exhaustion, constipation, nausea, vomiting, cramps, dyspepsia, difficulty urinating, daytime sleepiness, tachycardia, and rash were all recorded as signs and symptoms.

Data's normalcy was examined. Z test for difference between two proportions or Fisher's exact test for small sample size data were used to examine qualitative data.

Utilising the Z test for difference between two means, quantitative data was evaluated. P values <0.05 were deemed significant, whereas those over >0.05 were deemed non-significant. P values < 0.001 were deemed extremely significant.

Results

Age, sex, habits, systolic, diastolic, and heart rate baseline values for all two groups were equivalent (Table 1).

Table 1: Baseline data of Cilnidipine and amlodipine groups

Parameters	Cilnidipine (n=25) (Mean±SD)	Amlodipine (n=25) (Mean±SD)	p-value
Systolic Blood Pressure (mmHg)	155.03±8.89	155.79±8.77	p>0.05
Diastolic Blood Pressure (mmHg)	95.16±3.99	98.2±4.33	p>0.05
Heart Rate (bpm)	74.89±4.99	74.20±4.87	p>0.05

Table 2: Effect of drugs on mean systolic and diastolic blood pressure (mmHg) at 2, 4, 8 and 12 weeks.

Duration	Systolic BP (mean ±SD)		Diastolic BP (mean ±SD)	
	Cilnidipine (n=25)	Amlodipine (n=25)	Cilnidipine (n=25)	Amlodipine (n=25)
Baseline	155.03±8.89	155.79±8.77	95.16±3.99	98.2±4.33
2 weeks	143.03±6.55	144.76±7.05	89.01±2.99	89.44±3.02
4 weeks	138.59±6.56	140.99±7.00	86.22±2.65	87.00±2.70
8 weeks	133.16±6.01	135.72±6.49	83.71±3.64	84.12±3.10
12 weeks	131.4±4.86	133.4±7.51	83.64±3.37	84.63±3.43

Table 3: Comparison of mean reduction in systolic and diastolic blood pressure (mmHg) from the baseline

Duration	Systolic BP (mean ±SD)		Diastolic BP (mean ±SD)	
	Cilnidipine (n=25)	Amlodipine (n=25)	Cilnidipine (n=25)	Amlodipine (n=25)
2 weeks	11.99±3.31	10.98±3.95	9.17±1.76	8.00±2.01
4 weeks	15.2±3.90	15.78±3.65	11.0±2.02	10.50±2.60
8 weeks	21.75±4.25	20.0±+5.01	11.99±1.65	12.25±2.50
12 weeks	22.60±4.16	22.99±4.14	13.26±1.65	13.88±2.07

p- value : >0.05 in both groups

When compared to the pre-treatment data, the decrease in systolic blood pressure in the groups receiving cilnidipine and amlodipine was shown to be highly statistically significant ($p<0.001$) at 2, 4, 8 and 12 weeks of treatment (Table 2). When compared to the baseline values in both groups, the decrease in diastolic blood pressure was also discovered to be statistically significant ($p<0.001$) at 2, 4, 8 and 12 weeks of therapy.

Systolic blood pressure in the Cilnidipine group was reduced on average by 11.99±3.31 mmHg after two weeks, 15.2±3.90 mmHg after four weeks, 21.75±4.25 mmHg after eight weeks, and 22.60±4.16 mmHg after 12 weeks of treatment (Table 3).

While the amlodipine group experienced a mean drop in systolic blood pressure of 10.98±3.95 mmHg at two weeks, 15.78±3.65 mmHg at four weeks, 20.0±5.01 mmHg at eight weeks, and 22.99±4.14 mmHg at twelve weeks of treatment. There was no discernible difference between the two groups when the reduction in systolic blood pressure was examined ($p>0.05$). The average decrease in diastolic blood pressure in the cilnidipine group was 9.17±1.76 mmHg at two weeks, 11.0±2.02 mmHg at four weeks, 11.99±1.65 mmHg at eight weeks, and 13.26±1.65 mmHg at twelve weeks. Amlodipine group experienced a mean reduction in diastolic blood pressure of 8.00±2.01 mmHg at week 2, 10.50±2.60 mmHg at week 4, 12.25±2.50 mmHg at week 8, and 13.88±2.07 mmHg at week 12. The difference between these values when compared between the two groups was not statistically significant ($p>0.05$).

Table 4: Adverse drug reactions observed in both the groups.

Adverse Reactions	Cilnidipine (n=25)	Amlodipine (n=25)
Pedal edema*	1	4
Headache	1	2
Flushing	1	1
Tachycardia	-	1
Dizziness	-	1
Fatigue	1	1
Constipation	-	1
Total number of adverse reactions	2	9
Total number of patients showing adverse reactions	2	6

*P Value significant (<0.05).

Table 5: Effect of drugs on laboratory parameters and heart rate

Parameters	Cilnidipine (Mean±SD)		Amlodipine (Mean±SD)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Creatinine (mg/dl)	0.98±0.29	0.91±0.23	1.04±0.21	0.95±0.27
SGPT (IU/L)	21.63±6.97	21.11±6.34	23.29±5.81	23.92±5.51
SGOT (IU/L)	23.48±7.11	24.09±7.24	25.23±6.11	25.98±5.93
BSL (mg/dl)	99.42±8.33	98.42±8.72	98.99±9.94	99.74±8.99
Heart rate (bpm)	75.47±5.45	74.94±3.93	75.22±4.69	74.65±3.28

*P Value >0.05

3 patients in Cilnidipine group and 4 patients in amlodipine group not achieved target BP at the end of study.

These patients were labelled as non-responders. There was no statistical difference found in number of non-responders between two groups (p>0.05).

Peripheral edoema, headache, flushing, and weariness were adverse responses seen in the group treated with cilnidipine. In addition to these, patients using amlodipine also experienced tachycardia, vertigo, and constipation. According to table 4, 2 patients in the group receiving cilnidipine reported 3 adverse events, while 6 patients in the amlodipine group showed 9 adverse reactions. It was determined that the difference between the groups receiving cilnidipine and amlodipine in the number of patients reporting adverse reactions was statistically significant (p <0.05).

Peripheral edema, headache, and flushing were the two vasodilatory adverse responses that one patient in the cilnidipine group exhibited, whereas six individuals in the amlodipine group displayed eight side effects associated with vasodilation, including peripheral edoema, headache, flushing, dizziness, and tachycardia. One patient in the cilnidipine group reported having pedal edoema, whereas eight individuals in the amlodipine treatment group experienced pedal edoema. The incidence of pedal edoema was considerably higher in the amlodipine group when the two groups were compared (p<0.05). Between the two groups, there was no discernible change in the mean blood pressure of patients with or without pedal edoema (p>0.05). Even though the number of adverse events other than pedal edoema was higher in the amlodipine-treated group, comparisons revealed that this difference was not statistically significant (p>0.05) (Table 4).

Serum creatinine, SGPT, SGOT, random blood sugar level, and heart rate results for both groups are shown in Table 5 at the beginning and end of the study. These values did not significantly differ between the pre- and post-treatment periods (p>0.05).

Discussion

To maintain rigorous blood pressure control, the management of hypertension, a significant cardiovascular risk factor, basically necessitates lifetime medication therapy.[7] Better tolerated antihypertensive medicines are needed to increase drug treatment adherence.

Studies on CCBs' impact on cardiovascular safety have been conducted. One of the frequently noticed side effects of CCBs in the dihydropyridine category is pedal edoema. With very high doses of dihydropyridines, edoema may surpass 80% and is dose-dependent.[8] In its class, amlodipine is a well-known and often given medication. The tolerability patterns of several drugs in the

same class, however, can vary.[9] In order to compare Cilnidipine, a recently added dihydropyridine congener, with dihydropyridine amlodipine, a widely used dihydropyridine, this study was conducted.

This study shown that, in the majority of patients, cilnidipine dramatically decreased blood pressure within 15 days of medication compared to baseline. Cilnidipine's antihypertensive impact continued to increase during the course of the research. When Cilnidipine's antihypertensive efficacy was compared to that of amlodipine, both medications appeared to be similarly effective in lowering both systolic and diastolic blood pressure. Additionally, there was no statistically significant difference in the non-responders between the two groups.

Data pertaining to the two trial medications' tolerability are shown in Table 5. In the group receiving cilnidipine, 2 patients reported 3 adverse responses, whereas 6 individuals in the amlodipine group showed 9 adverse reactions. The difference between the two groups' patient reporting rates of adverse responses was statistically significant ($p< 0.05$).

Patients receiving Cilnidipine had reduced incidence of vasodilatory adverse effects than those receiving amlodipine in the study. Pedal edema showed the greatest difference in incidence among all side effects of vasodilation. Pedal edoema was reported by 1 patient in the cilnidipine group and 4 patients in the amlodipine group. It was determined that this difference was statistically significant ($p< 0.05$). Some of the earlier investigations have shown similar reports. In comparison to the Cilnidipine-treated group, the amlodipine-treated group saw considerably greater rates of edoema.[10] According to findings in a different trial, compared to the few second-generation calcium channel blockers, such as amlodipine, cilnidipine dramatically reduced the incidence of vasodilatory edoema for any given decline in blood pressure.

Given that both groups saw equal blood pressure reductions and that there was no difference in the amount of the antihypertensive impact in patients with or without edema, it is impossible to link this difference in edema incidence to the degree of blood pressure decrease.

The edoema develops as a result of capillary fluid filtration into the tissue's interstitial space. Normally, while moving from a supine to a standing position, postural vasoconstriction occurs in both the arteriolar and the venous limb of the blood vessels. The capillary fluid filtration is kept constant by this venoarteriolar reflex. CCBs specifically reduce the precapillary arteriolar vasoconstriction. They appear to suppress the reflex control of cutaneous blood flow known as the myogenic component, which is unaffected by neurological, metabolic, or other hormonal factors.[11] The intracapillary pressure may rise as a result, causing capillary fluid to filter into the interstitium. This causes edoema to form, which gravity appears to amplify.

Compared to prior CCBs, cilnidipine appears to have a different set of effects on the blood arteries. In addition to the kidney's afferent arteriole, experimental studies have demonstrated that cilnidipine also has a specific vasodilatory impact on the efferent arteriole.[12] It was therefore claimed that cilnidipine offers a more balanced pre- and postglomerular dilatation, lowering intracapillary pressure. The occurrence of edema would be reduced if a balanced vasodilator activity also occurred in other capillary beds, according to the theory.[10]

Other potential processes have been suggested by some studies. According to one theory, the lower sympathetic activation of lercanidipine results in less venoconstriction than other medications. By calculating the

norepinephrine levels in the serum, Fogari *et al*. examined this variation. Patients treated with cilnidipine demonstrated lower norepinephrine levels than those treated with nifedipine GITS, it was observed.[13] There has also been talk of a different impact on vascular permeability and subsequent fluid extravasation.[14] Another theory holds that Cilnidipine's improved tolerability profile results from a different pattern of pharmacological activity. Comparing cilnidipine to other long-acting dihydropyridines, it has been suggested that it has a higher solubility within the bilayer of artery cellular membrane. Even though it has a relatively short plasma half-life, this causes it to remain in the blood vessels for a longer period of time, leading to a longer duration of activity.

As a result, it was proposed that Cilnidipine quick clearance from plasma might be to blame for its positive tolerability profile.[15]

Although there was a lower incidence of side effects from vasodilation—aside from pedal edema in the Cilnidipine-treated group compared to the amlodipine group, the difference was statistically insignificant. This finding agreed with those of the ELYPSE and ELECTRA studies.[16,17]

In this investigation, no medicine had any negative effects on the measurements of serum creatinine, SGPT, SGOT, blood sugar level, or heart rate.

Other positive effects of cilnidipine have been noted in earlier research, in addition to the efficacy measures examined in the current investigation. Cilnidipine is equally successful in treating young and old people, according to human research, especially for treating isolated systolic hypertension.

Patients with concomitant illnesses including type 2 diabetes and/or renal failure benefit from it as well. Additionally stated Because of its favourable efficacy, cilnidipine looks to be well tolerated across all age groups. Cilnidipine is a flexible option for antihypertensive treatment across a wide spectrum of individuals, according to the results of the current study and observations from the earlier clinical trials [18].

Despite its benefits, one drawback of cilnidipine is that it is more expensive than amlodipine. The current study is a modest one in terms of both the scope and the number of patients involved. To fully understand the utility of this medicine in India, further thorough studies with a large number of patients with varying severity and comorbidities, taking into account more effectiveness metrics to assess long-term effect, and compliance are required.

Conclusion

Thus, it may be inferred that Cilnidipine is linked with a significantly reduced incidence of vasodilation-related adverse effects than amlodipine, particularly pedal edoema, for a comparable antihypertensive efficacy. This favourable tolerability profile may improve treatment outcomes by encouraging better medication therapy adherence.

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