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A Comparison Between Cilnidipine and Amlodipine for Efficacy and Tolerability in Patients with Essential Hypertension

KEYWORDS: Cilnidipine, Amlodipine, Essential Hypertension, Pedal edema

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ABSTRACT ***Background:*** *Cilnidipine, a newly added calcium channel blocker, was compared with Amlodipine for their efficacy and tolerability.*

Methods: *This was a prospective, double blind, parallel group study done in the Department of Pharmacology, ACSR Government Medical College, Nellore from June 2013-14. 100 patients according to inclusion and exclusion criteria were randomised into two groups of 50 each. One group received cilinidipine 10 mg while second group received tablet amlodipine 5 mg at the beginning, both once daily orally for 12 weeks of duration. Follow up was done at 2, 4, 8 and 12 weeks. Systolic and diastolic blood pressure was recorded in sitting position. If the patient did not attain target blood pressure of 140/90 mmHg, dose was titrated at 4, 8 weeks. Tolerability was assessed by questioning about adverse drug reactions at follow up and derangements of routine laboratory parameters at the end. Z test was used for analysis.*

Results: *There was no statistical difference between antihypertensive efficacies of two drugs. Number of patients showing adverse reactions were significantly less in cilnidipine group compared to amlodipine. Though vasodilation related adverse reactions were less in cilnidipine group, significant difference was observed only in occurrence of pedal edema. This difference in incidence of edema cannot be related to the extent of reduction in blood pressure.*

Conclusions: *With the comparable antihypertensive efficacy, cilnidipine is associated with considerably lower incidence of vasodilation related side effects than amlodipine, especially pedal edema. This favourable tolerability profile can potentially enhance treatment outcome by promoting better adherence to drug therapy.*

INTRODUCTION

Hypertension is a global health care problem. Since last few decades, prevalence of hypertension has increased in India, especially in urban population.[1] It is a well-recognised risk factor for the cardiovascular diseases.[2] It occurs commonly with diabetes, which itself is a major cardiovascular risk factor.[3]

Calcium channel blocker (CCB) class of drugs comprises three groups of compounds with distinct pharmacodynamics effect. Dihydropyridines group of CCBs are recognised as well tolerated and safe drugs. They are considered as one of the first line antihypertensive drugs. But the main troublesome adverse reactions of them are the development of pedal edema and other vasodilation related side effects like headache, dizziness, flushing, palpitation etc.[4] This poor drug tolerability can lead to poor compliance of the therapy. It is stated that one in four patients discontinue antihypertensive treatment within the first year of therapy because of adverse reactions.[5-7] Moreover, this edema may get worsen with time leading to hyperpigmentation and discoloration of skin. This can lead to dose reduction or prevent use of this effective class of drugs.

Cilnidipine is a derivative of third generation CCBs, claim to have even and sustained blood pressure lowering with once-daily dosing. Common adverse drug reactions related to CCBs such as pedal edema, headache, dizziness, palpitation etc. are said to be low with this vasoselective dihydropyridine congener. Very few clinical trials have been conducted comparing this drug with one of its older and time tested congener-amlodipine. As tolerability to antihypertensive may vary between populations, this study was undertaken to evaluate the efficacy and tolerability of Cilnidipine in patients of essential hypertension attending tertiary care hospital.

METHODS

This was a prospective, randomized, double blind, parallel group study carried out at a tertiary care hospital over a year after obtaining approval by institutional ethics committee. Newly diagnosed patients of both sexes and age more than 35 years with mild to moderate essential hypertension (systolic blood pressure between 140 and 179 mmHg and diastolic blood pressure between 90 and 109 mmHg) were enrolled in this study after receiving informed written consent. The following category of patients were excluded: patients on other anti-hypertensive drugs, secondary hypertension, obstructive biliary disease, cholestasis or hepatic impairment, renal impairment, aortic stenosis, unstable angina, uncontrolled heart failure and MI within 1 month of attack pregnant and lactating women, female patients of child bearing age group not using medically approved contraceptives.

100 patients attending OPD were screened; out of which 100 patients were enrolled in the study and were randomised into two groups of 50 each (Figure 1). Simple randomization was done and allocation was concealed by employing different investigators for each step of random number generation, enrolment, assignment of patients to treatment groups. Patients in first group received tablet Cilnidipine 10 mg while second group patients received tablet amlodipine 5 mg in the beginning, both once daily orally for 12 weeks of duration. Follow up was done at 2, 4, 8 and 12 weeks. At each visit, patients were clinically examined and medical history was noted. All patients advised lifestyle modifications. At each visit heart rate was noted, systolic and diastolic blood pressure (BP) was recorded in sitting position after 10 minutes of rest by auscultation method using mercury sphygmomanometer. The patients were advised to avoid smoking or drinking coffee within 30 minutes before assessment of BP. Laboratory in-

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vestigations like serum creatinine, SGOT, SGPT, random blood sugar level were carried out at first day and 12 weeks of study.

The primary efficacy parameters were the reduction in baseline systolic and diastolic BP. If the patient did not attain the target blood pressure of 140/90 mmHg, the dose was titrated at 4th and 8th weeks by 5mg and 2.5 mg in Cilnidipine and amlodipine groups respectively.

Patients who did not attain target BP level at the end of study were labelled as non-responders and referred to physician for further treatment. Tolerability and safety was assessed by presence or absence of adverse drug reactions, and derangement of laboratory parameters. Signs and symptoms namely pedal edema, headache, dizziness, flushing, palpitation, fatigue, constipation, nausea, vomiting, muscle cramps, dyspepsia, difficulty in micturition, day time sleepiness, tachycardia and rash were noted.

Data was checked for normality. Qualitative data was analysed by using Z test for difference between two proportions or Fisher's exact test for small sample sized data. Quantitative data was analysed using Z test for difference between two means. P value <0.05 was taken as significant and p value <0.001 was considered as highly significant; while p value >0.05 was regarded as non-significant.

RESULTS

Baseline values of all three groups were comparable with respect to age, sex, habits, systolic BP, diastolic BP and heart rate (Table 1).

Table 1: Baseline data of Cilnidipine and amlodipine groups.

	Cilnidipine	Amlodipine	
Parameters	n_1=55	n_2=45	p value
	(mean ±SD)	(mean ±SD)	
Systolic BP (mmHg)	156.04±9.52	156.81±9.42	p>0.05
Diastolic BP (mmHg)	97.15±4.21	97.5±4.44	p>0.05
Heart rate (bpm)	75.47±5.47	75.22±4.69	p>0.05

In both Cilnidipine and amlodipine treated groups, the reduction in systolic BP was found to be highly statistically significant (p<0.001) at 2, 4, 8 and 12 weeks of therapy, when compared with the baseline readings

(Table 2). The reduction in diastolic BP was also found to be statistically significant (p<0.001) at 2, 4, 8 and 12 weeks of therapy, when compared with the baseline readings, in both the groups.

The mean reduction in systolic BP in Cilnidipine group was 12.00±3.27 mmHg at 2 weeks, 16.4±3.45 mmHg at 4 weeks, 20.77±4.27 mmHg at 8 weeks and 23.6±4.14 mmHg at 12 weeks of treatment (Table 3). While the mean reduction in systolic BP in amlodipine group was 10.95±3.54 mmHg at 2 weeks, 15.79±3.55 mmHg at 4 weeks, 19.95±4.81 mmHg at 8 weeks and 22.81±4.12 mmHg at 12 weeks of treatment. When the reduction in systolic BP in two groups was compared, there was no significant difference between the two groups (p>0.05). The mean reduction in diastolic BP in Cilnidipine group was 8.17±1.52 mmHg at 2 weeks, 10.8±2.31 mmHg at 4 weeks, 12.44±1.75 mmHg at 8 weeks and 14.26±1.98 mmHg at 12 weeks. While the mean reduction in diastolic BP in amlodipine group was 8.09±1.92 mmHg at 2 weeks, 10.54±2.63 mmHg at 4 weeks, 12.36±2.25 mmHg at 8 weeks and 13.86±2.04 mmHg at 12 weeks. When these values were compared between two groups, the difference was not statistically significant (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_1=55	Amlodipine n_2=45	Cilnidipine n_1=55	Amlodipine n_2=45
Day 0	156.04±9.52	156.81±9.42	97.15±4.21	97.5±4.44
2 weeks	144.04±6.65	145.86±7.11	88.97±3.00	89.40±3.03
4 weeks	139.64±6.67	141.02±6.95	86.35±2.67	86.95±2.74
8 weeks	135.26±5.84	136.68±6.58	84.71±3.46	85.13±3.21
12 weeks	132.4±5.86	134±6.51	82.88±3.37	83.63±3.43

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

Duration	Systolic BP reduction (mean ±SD)		P value	Diastolic BP reduction (mean ±SD)		P value
	Cilnidipine n_1=55	Amlodipine n_1=45		Cilnidipine n_1=55	Amlodipine n_1=45	
2 weeks	12.00±3.27	10.95±3.54	p>0.05	8.17±1.52	8.09±1.92	p>0.05
4 weeks	16.4±3.45	15.79±3.55	p>0.05	10.8±2.31	10.54±2.63	p>0.05
8 weeks	20.77±4.27	19.95±+4.81	p>0.05	12.44±1.75	12.36±2.25	p>0.05
12 weeks	23.6±4.14	22.81±4.12	p>0.05	14.26±1.98	13.86±2.04	p>0.05

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

Adverse reactions	Cilnidipine	Amlodipine
	n_1=55	n_2=45
Pedal edema*	1	8
Headache	2	4
Flushing	1	2
Tachycardia	-	1
Dizziness	-	1
Fatigue	1	1
Constipation	-	1
Total number of adverse reactions	5	18
Total number of patients showing adverse reactions*	4	13

*P Value significant (<0.05).

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

Parameters	Cilnidipine n_1=55 (mean±SD)		p value		Amlodipine n_1=45 (mean±SD)		p value	
	Before treatment	After treatment			Before treatment	After treatment		
Creatinine (mg/dl)	0.98±0.29	0.91±0.23		p>0.05	1.04±0.21	0.95±0.27		p>0.05
SGPT (IU/L)	21.63±6.97	21.11±6.34		p>0.05	23.29±5.81	23.92±5.51		p>0.05
SGOT (IU/L)	23.48±7.11	24.09±7.24		p>0.05	25.23±6.11	25.98±5.93		p>0.05
BSL (mg/dl)	99.42±8.33	98.42±8.72		p>0.05	98.99±9.94	99.74±8.99		p>0.05
Heart rate (bpm)	75.47±5.45	74.94±3.93		p>0.05	75.22±4.69	74.65±3.28		p>0.05

6 patients in Cilnidipine group and 7 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).

In Cilnidipine treated group, adverse reactions noted were peripheral edema, headache, flushing and fatigue. In addition to these, amlodipine treated patient reported tachycardia, dizziness and constipation. As shown in table 4, 4 patients reported 5 adverse events in Cilnidipine treated group as compared to 13 patients showing 18 adverse reactions in amlodipine group. The difference in number of patients reporting adverse reactions between Cilnidipine and amlodipine group was found statistically significant (p <0.05).

3 patients in Cilnidipine group experienced 4 vasodilatory adverse reactions (viz. peripheral edema, headache and flushing) while in amlodipine group 11 patients showed 16 vasodilation related side effects (viz. peripheral edema, headache, flushing, dizziness and tachycardia). In Cilnidipine group, 1 patient had reported pedal edema while 8 patients had showed pedal edema in amlodipine treated group. When two groups were compared, the incidence of pedal edema was significantly higher in amlodipine group (p<0.05). There was no significant difference observed in mean blood pressure of patients with or without pedal edema within both the groups (p>0.05). Though numbers of various adverse effects other than pedal edema were more in amlodipine treated group, when this difference was compared, it was found non-significant (p>0.05) (Table 4).

Table 5 shows the values of serum creatinine, SGPT, SGOT, random blood sugar level and heart rate at the baseline and at the end of the study in both the groups. There was no significant differences observed in these values (p>0.05) before and after treatment.

DISCUSSION

Management of hypertension, a major cardiovascular risk factor, practically requires lifelong drug therapy to achieve strict blood pressure control.[8] To improve compliance of the drug treatment, better tolerated antihypertensive agents are required.

CCBs have been studied for its effect on the cardiovascular safety. Pedal edema is one of the commonly observed side effect with dihydropyridine group of CCBs. Edema is dose dependent, may exceed 80% with very high doses of dihydropyridines.[9] Amlodipine is a well-established and commonly prescribed drug in its class. But different tolerability pattern can be seen between compounds of the same class.[10] Therefore this study was undertaken to compare Cilnidipine, a newly added dihydropyridine congener, with commonly used dihydropyridine amlodipine.

This study showed that Cilnidipine significantly lowered blood pressure within 15 days of the therapy compared to base line in majority of the patients. A consistent increment in the antihypertensive action of Cilnidipine was observed throughout study period. When antihypertensive efficacy of Cilnidipine was compared with amlodipine, both drugs seem to be equally effective in reducing systolic and diastolic BP. The difference in non-responders between two groups was also statistically insignificant.

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Table 5 shows data related with tolerability of the two drugs in the study. 4 patients reported 5 adverse reactions in Cilnidipine treated group as compared to 13 patients showing 18 adverse reactions in amlodipine group. This difference in number of patients reporting adverse reactions between two group was statistically significant ($p < 0.05$).

In the study, patients treated with Cilnidipine had experienced lower rates of vasodilatory side effects than those who received amlodipine. Among all vasodilation related side effects observed, major difference in incidence was observed in pedal edema. In Cilnidipine group, 1 patient experienced pedal edema while 8 patients reported it in amlodipine treated group. This difference was found to be statistically significant ($p < 0.05$). Similar reports have been shown in some of the earlier studies. Leonetti et al. has found significantly higher rates of edema in amlodipine treated group compared to Cilnidipine.10 Observations in another study indicated that for any given fall in blood pressure, the incidence of vasodilatory edema was significantly less with Cilnidipine compared with the few second-generation calcium channel blockers including amlodipine.11 This difference in incidence of edema cannot be related to extent of reduction in blood pressure, as the magnitude of blood pressure reduction is similar in both the groups and no difference in magnitude of antihypertensive effect was observed in patients with or without edema.

The edema is outcome of capillary fluid filtration into the interstitial space of the tissue. Normally, postural vasoconstriction occurs in both the arteriolar and the venous limb of the blood vessels when there is a change from the supine to the standing position. This venoarteriolar reflex maintains the capillary fluid filtration constant. The precapillary arteriolar vasoconstriction is selectively diminished by CCBs. They appear to block the myogenic component of the reflex control of the cutaneous blood flow, which is independent of neural, metabolic, and other hormonal influences.12 This could be responsible for rise in intracapillary pressure, which results in capillary fluid filtration into the interstitium. This leads to formation of edema which seems to be exaggerated by gravity.

Cilnidipine seems to have different set of influence on the blood vessels compared to older CCBs. Experimental studies have shown that Cilnidipine also has a distinct vasodilatory effect on the efferent arteriole in addition to the afferent arteriole in the kidney.13 Thus, it was stated that Cilnidipine provides a more balanced pre- and postglomerular dilation, thereby reducing intracapillary pressure. It was hypothesized that such a balanced vasodilator action could take place in other capillary beds as well, which results in decreased incidence of the edema.11

Some studies have proposed other possible mechanisms. One hypothesis suggests that lercanidipine causes lesser venoconstriction than other drugs due to lower sympathetic activation. Fogari et al. studied this difference by estimating serum levels of norepinephrine. It was seen that Cilnidipine treated patients showed lesser norepinephrine levels than patients treated with nifedipine GITS.14 A different effect on vascular permeability and consequent fluid extravasation has also been suggested.15 Another hypothesis states that different pattern of pharmacological action of Cilnidipine is responsible for its favourable tolerability profile. Cilnidipine proposed to have a greater solubility within the arterial cellular membrane bilayer compared to other long acting dihydropyridines. This results in longer stay in the blood vessels and consequent long duration of action even though it has relatively short plasma half-life. Therefore it was suggested that rapid removal of Cilnidipine from plasma may be responsible for its favourable tolerability profile.16

Though incidence of vasodilation related side effects other than pedal edema were less in Cilnidipine treated group as compared to amlodipine group, the difference was statistically not significant. This observation was similar to the findings of the ELYPSE and the ELECTRA study.17,18

No drug had any adverse impact on the values of serum creatinine, SGPT, SGOT, blood sugar level and heart rate in this study.

Apart from the efficacy parameters studied in the present study, various other favourable effects of Cilnidipine have been observed in previous studies. Human studies have demonstrated that Cilnidipine is equally effective in young and old patients (especially in isolated systolic hypertension). It is also effective in patients associated with comorbid conditions such as type 2 diabetes and/or renal dysfunction.2 It is also stated

Therefore, Cilnidipine appears to be well tolerated in all age groups with favorable efficacy. Findings of the present study and observations from the previous clinical trials make Cilnidipine a flexible choice for antihypertensive treatment across a broad range of patients.

Despite its advantages, one disadvantage of Cilnidipine is its higher cost compared to amlodipine. The present study is a small study both as regards to the number of patients included and the duration. In India more extensive studies including large number of patients with differing severity and comorbidities; considering more efficacy parameters to evaluate long term effect and compliance are required to determine the exact utility of this drug.

Thus it can be concluded that, for the comparable antihypertensive efficacy, Cilnidipine is associated with considerably lower incidence of vasodilation related side effects than amlodipine, especially pedal edema. This favorable tolerability profile can potentially enhance treatment outcome by promoting better adherence to drug therapy.

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