e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(6); 2660-2668

Original Research Article

A Comparative Study of Efficacy and Safety of Cilnidipine with Amlodipine in Patients with Hypertension

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Received: 01-03-2026 / Revised: 15-04-2026 / Accepted: 21-05-2026
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Conflict of interest: Nil

Abstract

Background: Hypertension is a major public health problem and an important risk factor for cardiovascular and renal diseases. Calcium channel blockers are widely prescribed for its management. Cilnidipine, a dual L/N-type calcium channel blocker, has been proposed to offer advantages over the conventional L-type calcium channel blocker, amlodipine, particularly regarding sympathetic inhibition, renal protection, and a lower incidence of pedal edema.

Aim: To compare the efficacy and safety of cilnidipine with amlodipine in patients with essential hypertension.

Methods: A hospital-based, randomized, prospective, open-label observational study was conducted among 100 newly diagnosed hypertensive patients aged 35–75 years. Participants were randomly allocated to receive either amlodipine 10 mg or cilnidipine 10 mg once daily and were followed for 90 days. Blood pressure, heart rate, proteinuria, and adverse drug reactions were assessed at baseline and monthly follow-up visits. Statistical analysis was performed using SPSS version 21, with $p<0.05$ considered statistically significant.

Results: Both drugs effectively reduced blood pressure; however, cilnidipine produced significantly greater reductions in systolic, diastolic, and mean arterial pressure throughout follow-up. Cilnidipine also prevented reflex tachycardia, whereas heart rate increased in the amlodipine group. Urinary protein excretion decreased with cilnidipine but increased with amlodipine. Pedal edema was significantly less frequent with cilnidipine (6%) than with amlodipine (20%). Other adverse effects, including headache, giddiness, and nausea, were comparable between groups.

Conclusion: Cilnidipine demonstrated superior efficacy and safety compared with amlodipine in the management of essential hypertension. It provided better blood pressure control, reduced proteinuria, minimized reflex tachycardia, and was associated with a significantly lower incidence of pedal edema. Larger, long-term studies are recommended to validate these findings.

Keywords: Hypertension; Cilnidipine; Amlodipine; Calcium channel blockers; Proteinuria.

DOI: 10.25258/ijcpr.18.6.411

Introduction

Hypertension is the most common cardiovascular disease. The prevalence varies in different populations and ethnic groups, it is 29.8% in India. [1,2] In the Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), definitions of hypertension and pre-hypertension not addressed, but thresholds for pharmacologic treatment were defined.

According to it, antihypertensive medications (blood pressure medication) should be initiated in patients less than 60 years old if the systolic blood pressure is persistent>140 mmHg and the diastolic blood pressure is persistent>90 mmHg. If a patient is 60 years old and older, antihypertensive therapy should be initiated if the systolic blood pressure is >150 mmHg and the diastolic blood pressure is >90 mmHg. [3,4] Dihydropyridine-type calcium channel blockers (CCBs) are frequently used because of their strong BP-lowering properties and minimal adverse side effects. [5]

Both Amlodipine and Cilnidipine were reported to show equal efficacy in reducing blood pressure in hypertensive individuals. But Cilnidipine has certain advantages over amlodipine. As it is both N-type and L-type calcium channel blocker, it is said to be associated with lower incidence of pedal edema compared to only L-type channel blocker,

Amlodipine. The incidence of pedal edema with amlodipine has been found to be between 1.7% and 32% in different clinical studies.6 Almost 9.3% of patients discontinue amlodipine therapy due to the adverse effects, most commonly pedal edema. [7]

Further, Cilnidipine supposedly decreases the BP level without causing an increase in pulse rate, unlike Amlodipine and also causes a greater suppression of the increase in proteinuria and greater reduction in glomerular filtration rate than Amlodipine.8 Cilnidipine was also found to reduce triglycerides in hypertensive patients with diabetes mellitus. [9]

The current study is taken up in order to look into these advantages of Cilnidipine in comparison to Amlodipine, the calcium channel blocker that is routinely prescribed in clinical practice to patients with Hypertension, a major cardiovascular disease seen in the population and to see if it is a better alternative drug.

Aims and Objectives: To compare the efficacy and safety of calcium channel blocker Cilnidipine over Amlodipine in hypertension.

Patients and Methods: This was a Hospital based randomized, prospective, open label, observational study. This study was conducted among 100 patients attending the outpatient Department of General Medicine of Government Medical College, Kadapa for a period of one year after obtaining Institute Ethical Committee Certificate.

Patients were divided into two groups by randomized receive either Tab. Amlodipine 10 mg or Tab. Cilnidipine 10 mg orally once a day, in the morning.

Inclusion Criteria: Newly diagnosed adult patients of essential hypertension aged 35-75 years attending the OPD of General Medicine Department of Kadapa. Patients willing to give informed written consent for the study.

Exclusion Criteria: Patients aged <35 and >75 years of age, Pregnant and lactating women, Patients with recurrent symptomatic hypotension, Patients with a prior history of Angina/ Myocardial infarction/ Cerebro-vascular accidents/ Transient ischemic attack. Patients with uncontrolled diabetes mellitus, hepatic and renal impairment. Patients with severe hypertension. Patients not willing to give consent for the study.

Data Collection: The patients reviewed every 30 days, for a total of 4 visits, including a baseline for the study. Patient compliance assessed by pill count method on every visit. BP and Pulse rate recorded at the time of the scheduled visit. All BP measurements were taken in a seated position, having rested the patient for 10 minutes (WHO criteria). The blood pressure was measured in right arm, sitting posture by the auscultatory method using standard mercury sphygmomanometer. Three separate BP measurements were recorded with atleast 1 minute interval between the measurements. The mean of the three measurements was used as the BP value for that visit.

Pedal edema if any was assessed over the medial malleolus of both legs by applying pressure with right thumb for at least 2 seconds. If indention observed, it was recorded as pedal edema. Presence of pedal edema on either of the legs was considered as positive for the pedal edema. In proteinuric patients, urinary protein content was standardized for urinary excretion of 1g of creatinine.

Efficacy & Safety Parameters: The patients monitored for the following: Blood pressure- BP- Recorded at every visit and value noted. Pedal edema: Edema assessed by pressure with right thumb for at least 2 seconds over the medial malleolus of both legs. Pulse rate - Pulse rate taken at every visit and value recorded. Proteinuria- In proteinuric patients, urinary protein content standardized for urinary excretion of 1g creatinine.

Data Analysis: Collected data entered in Microsoft office excel 2007 and analysis done by Statistical Package for Social Sciences (SPSS) version 21. Relations between the groups with nominal data were tested with chi-square statistic and discrete data were tested with unpaired t-test statistic, findings with p-value <0.05 considered as statistically significant.

Results:

Table 1: Distribution by Mean Age of the Study Groups

Variable	Amlodipine Group	Cilnidipine Group	t-value	P value
Age (Mean±Std deviation in years)	46.6±7.81	47±7.62	0.259	0.796 (NS)

Table 2: Gender Wise Distribution of the Study Participants

Gender	Amlodipine Group	Cilnidipine Group	X^2 value	P value
Male	31 (62%)	30 (60%)	0.042	0.838 (NS)
Female	19 (38%)	20 (40%)		

Table 3: Distribution of Mean Duration of HTN among the Groups

Mean duration of HTN (in years)			
Amlodipine Group	**Cilnidipine Group**	**t-value**	**P value**
4.68±1.97	4.84±2.01	0.402	0.689 (NS)

Table 4: Distribution of the Study Participants by Association with Diabetes

Association with DM	Amlodipine Group	Cilnidipine Group	X^2 value	P value
Yes	29 (58%)	28 (56%)	0.041	0.840 (NS)
No	21 (42%)	22 (44%)		

Table 5: Distribution by Mean Weights of the Patients between the Groups

Variable	Amlodipine Group	Cilnidipine Group	t-value	P value
Weigh (Mean ± Std deviation in Kilograms)	58.74±3.83	57.78±3.85	1.25	0.214 (NS)

Table 6: Comparison of Heart Rates between the Groups

Heart Rate at	Amlodipine group	Cilnidipine group	t-value	P value
Baseline	77.2±7.95	77±9.53	0.114	0.91 (NS)
30 days	79.36±9.07	77.84±7.98	0.890	0.376 (NS)
60 days	80.76±6.61	77.02±7.30	2.685	0.008 (S)
90 days	83.16±7.44	76.44±7.36	4.54	<0.001 (HS)

Table 7: Comparison of SBP between the Groups

SBP	Amlodipine group	Cilnidipine group	t-value	P value
Baseline	163.46±10.85	164.5±10.18	0.494	0.622 (NS)
30 days	158.8±12.41	145.72±13.25	5.095	<0.001 (HS)
60 days	149.28±14.85	139.72±16.62	3.033	0.003 (S)
90 days	144.28±15.61	134.08±15.69	3.259	<0.001 (HS)

Table 8: Comparison of DBP between the Groups

DBP at	Amlodipine group	Cilnidipine group	t-value	P value
Baseline	100.6±5.27	101.3±5.25	0.665	0.507 (NS)
30 days	96.1±4.57	91.6±3.98	5.25	<0.001 (HS)
60 days	92.7±3.35	86.7±3.11	9.28	<0.001 (HS)
90 days	86.9±2.32	82.9±2.62	8.08	<0.001 (HS)

Table 9: Comparison of Mean Arterial Pressure (Map) Between the Groups

MAP at	Amlodipine group	Cilnidipine group	t-value	P value
Baseline	121.6±6.69	122.4±6.42	0.610	0.543 (NS)
30 days	116.9±6.63	109.6±5.83	5.847	<0.001 (HS)
60 days	111.5±6.01	104.4±5.96	5.931	<0.001 (HS)
90 days	106.1±5.61	99.9±5.86	5.404	<0.001 (HS)

Table 10: Distribution by Adverse Effects Observed During Follow-Up

Adverse effects	Amlodipine group	Cilnidipine group	X^2 value	P value
Pedal edema	10 (20%)	3 (6%)	4.332	0.03 (S)
Headache	5 (10%)	1 (2%)	2.837	0.09 (NS)
Giddiness	2 (4%)	1 (2%)	0.344	0.558 (NS)
Nausea	4 (8%)	1 (2%)	1.895	0.169 (NS)

Table 11: Comparison by the Level of Proteinuria between the Groups

Mean proteinuria	Amlodipine group	Cilnidipine group	t-value	P value
Baseline	0.86±0.29	0.94±0.23	1.53	0.130 (NS)
30 days	0.98±0.24	0.87±0.26	2.349	**0.03 (S)**
60 days	1.13±0.16	0.85±0.22	7.571	**<0.001 (HS)**
90 days	1.38±0.13	0.84±0.21	16.60	**<0.001 (HS)**

Discussion

Hypertension is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. Lifestyle changes and medications can lower blood pressure and decrease the risk of health complications. Lifestyle changes include weight loss, physical exercise, decreased salt intake, reducing alcohol intake and a healthy diet. If lifestyle changes are not sufficient then blood pressure medications are used. Dihydropyridine group of calcium channel blockers (CCBs) is most commonly used antihypertensive agents to treat essential hypertension. According to JNC-8, calcium channel blockers are the first line antihypertensive drugs. [10]

In the studies conducted, it was seen that Cilnidipine is a better tolerable drug. Hence this study was taken up to compare the efficacy and safety of calcium channel blocker Cilnidipine over Amlodipine. This is a hospital-based randomized control trail done on hypertensive patients attending medical OPD of GGH, Kadapa. For that, a total of 100 patients were recruited and grouped into two groups with 50 each. The first group received Tab. Amlodipine 10 mg and the second group received Tab. Cilnidipine 10 mg orally once a day in the morning.

Age: In the present study mean age of the patients treated with Amlodipine was 46.6±7.81 years and with Cilnidipine 47±7.62 years. On assessing the difference in the mean age between the two groups with t-test, it is not significant statistically. (t=0.259; p>0.05). This correlates with the study conducted by K. Anantha Babu et al [11] mean age was 55.2±7.89 years in Amlodipine group and 52.7±6.74 years in Cilnidipine group.

Ramya Y S et al [12] the mean age 55.75 ± 9.7 years in the Amlodipine group and 53.45 ± 8.9 years in Cilnidipine group. Kiran Shetty et al36 the mean age was 57.96±8.6 years and 57.79±10.07 years in Amlodipine and Cilnidipine groups respectively and also was not showing a significant difference between these two groups.

Gender: In the present study, out of 50 patients in the amlodipine group, 62% were males and 38% were females. Similarly, in Cilnidipine group, 60% were males and 40% were females. On assessing the gender wise difference between the two groups with the chi-square test, no statistical significance was observed. (X2=0.042; p>0.05).

In a study done by K. Anantha Babu et al [11] males (40%) and females (60%) in two groups. They recruited a number of females than males unlike in the present study. In a study done by Ramya Y S32 et al 63.3% of males and 36.7% of females in Amlodipine group and 73.3% of males and 26.7% of females in Cilnidipine group. In a study done by Kiran Shetty et al [13] males and females in Amlodipine group was 61.43% and 38.57% respectively and in Cilnidipine group was 52.86% and 47.14% respectively. The difference between the groups was not significant statistically. As in the present study in all these studies, gender matching was done to avoid the influence of gender on the efficacy of the drugs tested.

Mean duration of hypertension: In the current study mean duration of hypertension among patients in Amlodipine group was 4.68±1.97 years and among patients in Cilnidipine group were 4.84±2.01 years. On assessing the difference in the mean duration of hypertension between the two groups with t-test, it is not significant statistically. (t=0.402; p>0.05). The studies of Prabhakar Adake et al [14] included newly diagnosed (duration of <1 year) hypertensive patients to compare the efficacy of drugs Amlodipine and Cilnidipine. In order to avoid mixed effects, they advised the patients to stop the regular treatment for at least 2 weeks before starting the prescribed therapy for the study.

Association with Diabetes mellitus: In this study, around 58% patients in the Amlodipine group and 56% of the patients in the Cilnidipine group were also suffering from Diabetes mellitus i.e., more than half of the patients in each group suffering from Diabetes mellitus also. On assessing the difference between the two groups with t-test, it is not significant statistically. (X2=0.041; p>0.05). In a study done by Shunichi Kojima et 42.9% of patients were also associated with diabetes in Amlodipine group and 71.4% in Cilnidipine group, but the difference in the number of patients associated with diabetes mellitus was not significant between these two groups. (p>0.05).

In a study done by Zaman ZA et al [15] to know the effects of amlodipine and cilnidipine on blood pressure, heart rate, proteinuria, and lipid profile in hypertensive patients, a similar number of hypertensive patients associated with diabetes were included.

In a study done by Kiran Shetty et al [13] on clinical and biochemical parameters in Amlodipine and Cilnidipine treated hypertensive patients, on assessing their diabetic history, it was shown that there was no significant difference between the groups.

In a study done by Manjushree Mohanty et al [16] in Amlodipine group, 36.7% of patients were diabetics and in Cilnidipine group they were around 40%.

The presence of hypertension in diabetic patients substantially increases the risks of coronary heart disease, stroke, nephropathy, and retinopathy. When HTN coexists with DM, the risk of CVD is increased by 75%, which further contributes to the

overall morbidity and mortality of an already high-risk population. Generally, HT in type 2 diabetic person clusters with other CVD risk factors such as microalbuminuria, central obesity, insulin resistance, dyslipidemia, hypercoagulation, increased inflammation and left ventricular hypertrophy. [17]

This clustering risk factor in diabetic patients ultimately results in the development of CVD, which is the major cause of premature mortality in patients with type 2 DM. DM and HTN are interrelated diseases that strongly predispose people to atherosclerotic cardiovascular disease, and hence have been referred to as "the bad companions". [18]

Mean weight: In this study mean weight of the patients in the amlodipine group was 58.74±3.83 kilograms and in Cilnidipine group was 57.78±3.85 kilograms. On assessing the difference in mean weight between two groups with t-test, it is not significant statistically. ($t=1.25$; $p>0.05$). In a study done by Shunichi Kojima et al [19] mean weight of the patients in Amlodipine group was 61.0±3.0 and in Cilnidipine group was 61.6±1.9 with no statistical difference.

In a study done by Zaman ZA et al [15] mean BMI of the patients in Amlodipine group was 24.0±3.0 and in Cilnidipine group was 23.0±2.6. These two groups were not showing any significant difference with respect to mean BMI.

Obesity and overweight may have a major role in impairing renal pressure natriuresis in persons with chronic hypertension. [20] The blood-pressure-lowering effect of weight loss probably results from an improvement in insulin sensitivity and a reduction in sympathetic nervous system activity. Thus in the present study, the patients were allocated into two groups in such a way that, they were not differing much in basic characteristics such that age, gender, mean weight, Mean duration of hypertension and association with Diabetes mellitus. So the effects of these drugs can't be masked by these confounding factors.

In a study done by Adake P et al [14] to know the efficacy and incidence of pedal edema with Amlodipine and Cilnidipine in mild to moderate hypertensive individuals, 60 patients were recruited with age and gender matching between the groups.

In a study done by Zaman ZA et al [15] to know the effects of amlodipine and cilnidipine on blood pressure, heart rate, proteinuria, and lipid profile in hypertensive patients also included patients for study with age, gender and BMI matching between the groups.

Heart rate change with treatment: In the present study on the comparison of mean heart rate changes in two groups with the treatment, in amlodipine group, it is increasing from baseline to 90 days, but in Cilnidipine group, initially it shows elevation, but after 30 days it shows a declining trend. At the baseline, the mean heart rate difference between the groups is not significant statistically. ($t=0.114$; $p>0.05$)

The increase in heart rate from baseline to 90 days treatment was 5.96 beats per minute in Amlodipine group and the decrease in heart rate from baseline to 90 days treatment was 0.56 beats per minute in Cilnidipine group. Though the decrease in heart rate observed in Cilnidipine group was less, on a long period of use it may cause a significant decrease in heart rate.

At 30 days after the treatment also, the mean difference in heart rate between the groups is not significant statistically. ($t=0.890$; $p>0.05$). But at 60 days after the treatment, the difference in the mean heart rate between the groups is found to be statistically significant. ($t=2.685$; $p<0.05$). At 90 days after the treatment, the difference in the mean heart rate between the groups is significant statistically. ($t=4.54$; $p<0.05$). It shows that treatment with Cilnidipine will reduce the heart rate to the normal level better than Amlodipine and is a better alternative.

In a study done by Zaman ZA et al [15] nighttime Pulse Rate after treatment was significantly higher than that before treatment and daytime Pulse Rate after treatment tended to be higher than those before treatment. There was a significant decrease in the daytime and nighttime Pulse Rate in the Cilnidipine treatment group.

In a study done by Kiran Shetty et al [13] pulse rate of the patients who were on amlodipine and Cilnidipine respectively for more than 6 months showed nil significant difference in pulse rate. This may be due to the cross-sectional nature of the study and also may be due because the patients were on respective medications for more than 6 months. Epidemiological studies have demonstrated that a higher heart rate is associated with a long-term risk of cardiovascular mortality, independent of other cardiac risk factors. [21]

Systolic blood pressure change with treatment: In the present study on the comparison of systolic blood pressure changes in two groups, in amlodipine group, it declined slowly from baseline to 90 days, but in Cilnidipine group, the decline was rapid compared to amlodipine group. Cilnidipine is a better drug compared to Amlodipine in controlling systolic blood pressure. Reduction in the systolic blood pressure from baseline to 90 days treatment was 19.2 mm of Hg in Amlodipine group and 30.4 mm of Hg in Cilnidipine group. The reduction is significantly more in Cilnidipine group than Amlodipine group. ($p<0.05$)

At the baseline, mean systolic blood pressure difference between the groups is not significant statistically. (t=0.494; p>0.05). At 30 days after the treatment, mean systolic blood pressure difference between the groups is significant statistically. (t=5.095; p<0.05). At 60 days after the treatment, mean systolic blood pressure difference between the groups is significant statistically. (t=3.033; p<0.05). At 90 days after the treatment, mean systolic blood pressure difference between the groups is significant statistically. (t=3.259; p<0.05).

A recent clinical trial demonstrated that lowering of BP was associated with a significant fall in cardiovascular event. In a study done by Kiran Shetty et al [13] it was reported that Cilnidipine group has better control over-systolic blood pressure than the amlodipine group.

In a study done by Ramya Y S [12] et al it was reported that there was a statistically significant decrease in the level of both systolic and diastolic blood pressure in the Cilnidipine group compared to the Amlodipine group (P<0.05) at Day 90.

In a study done by Zaman ZA et al [15] it was noted that once daily use of Amlodipine or Cilnidipine significantly reduced the SBP. They found that Cilnidipine but not Amlodipine significantly decreased the BP level without causing an increase in Pulse Rate.

There have been previous reports which compared the effects of Amlodipine and Cilnidipine. There was a significant negative correlation between the degree of SBP change and that of PR change after Cilnidipine treatment. This finding is in agreement with several previous studies in which Cilnidipine suppressed sympathetic nervous activity, especially under a stress-induced hyperactive condition. [22]

Diastolic blood pressure change with treatment: In the present study on the comparison of diastolic blood pressure changes in two groups, in the amlodipine group, it declined slowly from baseline to 90 days, but in Cilnidipine group, the decline is rapid. Cilnidipine is a better drug compared to Amlodipine in controlling diastolic blood pressure.

Reduction in the diastolic blood pressure from baseline to 90 days of treatment was 13.7 mm Hg in Amlodipine group and 18.4 mm Hg in Cilnidipine group.

Though the reduction is more in Cilnidipine group than Amlodipine group, the difference is not significant statistically. (p>0.05). At the baseline, mean diastolic blood pressure difference between the groups is not significant statistically. (t=0.665; p>0.05). At 30 days after the treatment, mean diastolic blood pressure difference between the groups is significant statistically. (t=5.25; p<0.05). At 60 days after the treatment, mean diastolic blood pressure difference between the groups is significant statistically. (t=9.28; p<0.05). At 90 days after the treatment, mean diastolic blood pressure difference between the groups is significant statistically. (t=8.08; p<0.05)

These findings correlate with the findings of the study done by Kiran Shetty et al [13] reported that Cilnidipine group has better control over diastolic blood pressure than amlodipine group.

In Ramya Y S [12] et al study, it was reported that once-daily use of Cilnidipine significantly reduced the BP compared to Amlodipine without causing an increase in PR. This is relevant because various studies have demonstrated that a higher heart rate is associated with a long-term risk of cardiovascular mortality, independent of other cardiac risk factors.

In a study done by Zaman ZA et al [15] reported that once daily use of Amlodipine or Cilnidipine significantly reduced the DBP in both the groups. They didn't notice any difference between the groups in a reduction in DBP.

The antihypertensive effect of CCBs depends on their mechanism of action. Amlodipine is the third generation CCB which acts on L-type of calcium channels at vascular smooth muscles and relaxes the vascular smooth muscles and by this action reduces the peripheral vascular resistance; this leads to a reduction in blood pressure. [23]

In the present study, we found that the patients in the Cilnidipine treated group showed better blood pressure control than the amlodipine group.

Mean arterial pressure change with treatment: In the present study, on a comparison of mean arterial pressure changes in two groups with the treatment, in amlodipine group, it is declining slowly from baseline to 90 days, but in Cilnidipine group, the decline is rapid compared to amlodipine group. Cilnidipine is better drug compared to Amlodipine in controlling Mean arterial pressure. Reduction in the mean arterial pressure from baseline to 90 days treatment was 15.5 mm Hg in Amlodipine group and the reduction in mean arterial pressure from baseline to 90 days treatment was 22.5 mm Hg in Cilnidipine group. The reduction is significantly more in Cilnidipine group than Amlodipine group. (p<0.05).

At the baseline, the mean arterial pressure difference between the groups is not significant statistically. (t=0.610; p>0.05). At 30 days after the treatment, the mean arterial pressure difference between the groups is significant statistically. (t=5.847; p<0.05). At 60 days after the treatment, the mean arterial pressure difference between the groups is significant statistically. (t=5.931; p<0.05). At 90 days after the treatment, the mean arterial pressure difference between the groups is significant statistically. (t=5.404; p<0.05). In a study done by Shunichi Kojima et al [19] mean

arterial pressure noted were between 96–99 mmHg range throughout the follow-up period and showed no significant difference between the two groups.

In a study done by Ranjan Shetty et al [24] they have observed that mean arterial pressure was elevated in follow-up period by about 1.5 mm Hg from the baseline, but this difference was not significant. This is in contrary to the present study, may be due very short follow-up period of 4 weeks.

Proteinuria: In the present study, proteinuria of the patients could be standardized for urinary excretion of 1g creatinine. Mean protein excretion difference between the groups was not significant at baseline ($p>0.05$). After treatment, at 30 days, 60 days and 90 days, mean protein excretion difference was significant ($p<0.05$).Because with the treatment, mean protein excretion in Amlodipine group was increased, but in Cilnidipine group mean protein excretion was decreased. It shows Cilnidipine is a better drug to prescribe for hypertensive patients presenting with proteinuria. Compared to baseline values, mean protein excretion is significantly more in Amlodipine group (Anova=54.533; $p<0.001$), and the same is less in Cilnidipine group but not significant. (Anova=1.799; $p=0.149$). In a study done by Zaman ZA et al. to know the effects of Amlodipine and cilnidipine on blood pressure, heart rate, proteinuria and lipid profile in hypertensive patients, it was also reported similarly that with amlodipine treatment urinary protein excretion has increased and with Cilnidipine treatment protein excretion has decreased, but on comparison with baseline level the difference was not significant. Blood pressure control is important in suppressing the onset of renal dysfunction.

It was reported that antihypertensive therapy suppressed the progression of renal dysfunction. Regarding glomerular kinetics, it has been shown that inhibition of angiotensin II suppresses the elevation of glomerular pressure. Among CCBs, Cilnidipine has been reported to reduce glomerular pressure. [25]

Adverse drug reactions during follow-up: In the present study, a number of patients in Amlodipine group (42%) have reported with adverse drug reactions compared to Cilnidipine group (12%). In both the groups, most common adverse drug reactions were pedal edema (reported in frequencies of 20% in Amlodipine group and 6% in Cilnidipine group). The difference in reported frequency of pedal edema was significantly high in Amlodipine group compared to Cilnidipine group ($p<0.05$).

In a study done by Ramya YS et al [12] around 36% of the patients in Amlodipine group experienced adverse drug reactions like pedal edema, headache, nausea and giddiness and only 10% of the patients in the Cilnidipine group experienced adverse drug reactions like pedal edema, giddiness, and generalized rash. Most common adverse drug reactions in both the groups was pedal edema with the frequency of 15% in Amlodipine group and 7% in Cilnidipine group. These findings correlate with the current study.

In a study done by Adake P et al [14] in Cilnidipine group 6.66% of the patients presented with edema within 2 weeks of therapy, whereas in amlodipine group 63.3% patients presented with edema within 2 weeks of therapy. Cilnidipine has shown a significant reduction in the incidence of pedal edema when compared to amlodipine ($p<0.05$). These findings were similar to the present study.

In a study done by Manjushree Mohanty et al, [16] it was reported that Amlodipine treatment produced significantly more pedal edema than Cilnidipine. They also mentioned probable reasons for pedal edema due to CCBs as follows,

In normal individual precapillary vasoconstriction in response to venous congestion protects the capillary bed from increased blood pressure, thus restricts hydrostatic filtration of fluid into the interstitium. L-type CCBs like Amlodipine directly inhibit pre-capillary constriction and causes arteriolar dilatations and thus leads to interstitial oedema. L-type CCB's like Amlodipine cause dilatation of precapillary resistance vessels with sparing of postcapillary vascular tone causing capillary hypertension and filtration of fluid into interstitium. Increased microvascular permeability which causes extravasation of plasma protein and water into the interstitial space. This edema is not relieved by diuretics but can be reduced to some extent with ACE inhibitors and ARBs, which proves the fact that edema with Amlodipine is not the result of fluid retention. The risk of developing pedal edema while using CCB therapy appears to be higher in women, older patients, those with heart failure, upright postures, and those in warm environment.

The exact cause of more incidence of pedal edema in the female is unclear but it may be due to more self-examination, intolerance to a cosmetic problem or due to associated idiopathic edema (also known as cyclical edema, periodic edema, and the fluid retention syndrome). It is a poorly understood syndrome occurring almost exclusively in women. It is characterized by complaints of intermittent swelling of the face, trunk, and limbs and by weight variation unrelated to the menstrual cycle.

There is evidence of increased capillary permeability in idiopathic edema which leads to extravasations of fluid from the vascular compartment in the upright posture with secondary retention of sodium and water through the renin-angiotensin-aldosterone pathway. In the present study, the rate of incidence of a headache is high in

Amlodipine group. In the present study, the incidence rate of giddiness is more in Amlodipine group (4%) than Cilnidipine group (2%). But the difference between the groups is not significant. Similarly, Manjushree Mohanty et al [16] also reported in their study on evaluation of Safety and Tolerability of Amlodipine and Cilnidipine. In a study done by Ramya YS et al [12] 3% of the patients in Amlodipine group complained of dizziness and 2% of the patients in Cilnidipine group complained of dizziness. In the present study nausea and vomiting were observed more in Amlodipine group (8%) than Cilnidipine group, but the difference is not significant. ($p>0.05$).

In a study done by Ramya YS et al [12] to assess the effectiveness and safety of Cilnidipine versus Amlodipine in patients with newly diagnosed essential hypertension, 8% of the patients in Amlodipine group complained of nausea and vomiting and none of the patients in Cilnidipine group complained of nausea and vomiting.

Conclusions:

The present study aims at knowing the efficacy and safety of calcium channel blocker Cilnidipine over Amlodipine in hypertension.

The study was taken up to know the efficacy and safety of the drugs Cilnidipine and Amlodipine in hypertension the patients were enrolled into two groups at each with age and gender matching. They were also matched in the duration of hypertension, association with diabetes mellitus and weight of the patients.

The main findings of the present study are, The heart rate of the patients in Amlodipine group shows elevation with the treatment compared to the baseline value (77.2 bpm to 83.16 bpm) and in Cilnidipine group (77 bpm to 76.44 bpm) shows a decrease in heart rate. After 60 days of treatment, these two groups show a significant difference in change in heart rate. Systolic blood pressure of the patients in both the groups shows a decrease with the treatment compared to baseline value, but the decrease in SBP is rapid with Cilnidipine. (19.2 mm Hg change in Amlodipine group and 30.4 mm Hg change in Cilnidipine group)

Diastolic blood pressure of the patients in both the groups shows a decrease with the treatment compared to baseline value, but the decrease in DBP is rapid with Cilnidipine. (13.7 mm Hg change in Amlodipine group and 18.4 mm Hg change in Cilnidipine group) Similarly, mean arterial pressure of the patients in both the groups show a decrease with the treatment compared to baseline value, but the decrease in MAP is rapid with Cilnidipine. (15.5 mm of Hg change in Amlodipine group and 22.5 mm of Hg change in Cilnidipine group) Most common adverse effects of both the drugs are pedal edema; it is common in Amlodipine group (20%) than Cilnidipine group (6%). Other adverse effects like a headache, giddiness, and nausea were also reported in both groups.

Levels of protein excretion in urine started increasing in Amlodipine group with treatment compared to the baseline value (0.86 gms to 1.38 gms), but Cilnidipine decreases the excretion of protein in the urine (0.94 gms to 0.84 gms).

Further studies on a larger population for an extended period are needed to confirm these findings.

Recommendations: The following recommendations are suggested based on study findings: Amlodipine and Cilnidipine are good in reducing both the systolic and diastolic blood pressure. Cilnidipine is good in reducing the blood pressure without elevating the heart rate, unlike Amlodipine. So Cilnidipine is good in hypertensive patients with a cardiac abnormality. Cilnidipine will reduce the urinary excretion of protein, so it's a better tolerable drug in renal abnormality patients than Amlodipine. Cilnidipine has minimal adverse effects than Amlodipine.

Overall, Cilnidipine can be a better therapeutic option than amlodipine. Cilnidipine showed better safety and efficacy compared to Amlodipine. Cilnidipine is not found to be associated with producing reflex tachycardia. It can be beneficial in peripheral edema and proteinuria too.

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