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Original Research Article

Comparing the Effectiveness and Safety of Amlodipine vs. Cilnidipine for Mild to Moderate Hypertension

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Abstract

Background: Calcium channel blockers, including the recently developed cilnidipine, are widely used as first-line medications for treating newly diagnosed cases of primary essential hypertension. Cilnidipine has a unique advantage compared to amlodipine, another common calcium channel blocker. While amlodipine only targets L-type calcium channels, cilnidipine can target both L and N-type channels. This study aimed to compare the effectiveness and safety of these two medications in patients with essential hypertension.

Methods: A total of n=80 cases of mild to moderate hypertension were randomly allocated to two groups. Group I n=40 received a daily dose of Amlodipine 5mg, whereas those in Group II n=40 received Cilnidipine 10mg once daily, 30 minutes after breakfast, for 8 weeks. Participants were prohibited from using any other medications during the study period. Each patient underwent three visits: a baseline visit (Visit 0) on recruitment day, visit 1 after 30 days of medication, and Visit 2 after 60 days of treatment. Systolic and diastolic blood pressures, as well as heart rate, were measured at each visit. Clinical and laboratory parameters were reassessed at the end of the 8 weeks.

Results: Both medications significantly reduced Systolic and Diastolic Blood Pressure (SBP and DBP) and heart rate in both groups over 8 weeks.While Group II (Cilnidipine) consistently showed slightly lower blood pressure and heart rate, these differences were statistically insignificant, suggesting similar effectiveness between the two medications in this study.Both groups reported mild/moderate adverse events, with Group I having a consistently higher number and wider range of events compared to Group II.The most common events were fatigue and headache, with Group I experiencing additional events like headache + GI upset, vomiting, and ankle edema.

Conclusion: Both the calcium channel blockers amlodipine and cilnidipine exhibit equivalent efficacy in reducing systolic and diastolic blood pressure in patients with mild to moderate essential hypertension. Cilnidipine, as a fourth-generation calcium channel blocker, offers a promising pharmacological profile. In addition to its blood pressure-lowering effects, cilnidipine demonstrates notable safety and provides additional benefits including renoprotective, cardioprotective, and neuroprotective effects.

Keywords: Amlodipine, Cilnidipine, Hypertension, Systolic Blood Pressure, Diastolic Blood Pressure, Calcium Channel Blockers.

Introduction

Hypertension (HTN) stands as one of the most prevalent ailments globally, posing significant morbidity, mortality, and socioeconomic burden, thereby constituting a critical public health concern [1]. HTN is characterized by blood pressure (BP) levels at which initiating therapy diminishes BP-related morbidity and mortality [2]. The severity of HTN is categorized into mild/Stage/Grade 1 (systolic BP [SBP] between 140 and 159 and diastolic BP [DBP] between 90 and 99), moderate/Stage/Grade 2 (SBP between 160 and 179 and DBP between 100 and 109), and severe/Stage/Grade 3 (SBP ≥180 and DBP ≥110) [3]. Untreated HTN doubles the risk of cardiovascular diseases, encompassing coronary heart disease, congestive heart failure, stroke (both ischemic and hemorrhagic), renal failure, and peripheral arterial disease [4,5]. The extensive literature underscores the importance of stringent BP control for maximal reduction in clinical cardiovascular endpoints. Recent research suggests that a mere 2-mmHg reduction in average DBP correlates with a 14% decrease in the risk of stroke and ischemic events, alongside a concomitant 6% decline in the risk of coronary artery disease development [6-8].

Diuretics, α-blockers, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARBs), and calcium channel blockers (CCBs) constitute the primary classes of drugs used for hypertension management [4]. Of these, CCBs have emerged as pivotal agents for initial antihypertensive monotherapy, with dihydropyridines being the most frequently prescribed group in China and other Eastern Asian nations [9]. Amlodipine, a third-generation dihydropyridine, exhibits remarkable pharmacokinetic and pharmacodynamic characteristics, including slow absorption, prolonged plasma half-life, and reduced reflex tachycardia, rendering it a preferred choice [10]. However, a significant drawback associated with amlodipine is ankle edema, which leads to treatment discontinuation in approximately 9.3% of patients [10]. In contrast, cilnidipine represents a novel and distinctive dihydropyridine derivative CCB blocker with potent inhibitory effects on both L-type and N-type voltage-dependent calcium channels. Unlike other dihydropyridines, cilnidipine suppresses sympathomimetic activity, resulting in a lower incidence of ankle edema than amlodipine. Thus, this prospective study aimed to compare the efficacy of cilnidipine and amlodipine in hypertensive patients to contribute to the optimization of treatment strategies for HTN.

Material and Methods

This cross-sectional study was conducted in the Department of Medicine, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, UP. Institutional Ethical approval was obtained for the study. Written permission was obtained from all the participants of the study after explaining the nature of the study in the vernacular language. Those voluntarily willing to participate in the study were included.

Inclusion Criteria

1. Newly diagnosed hypertension as stage 1 and stage 2 as per JNC criteria 8. [3]
2. Aged 25 years and above
3. Males and females
4. Willing to participate in the study voluntarily

Exclusion criteria

1. Secondary hypertension
2. History of severe hepatic, renal disease, and severecardiac disease.
3. Pregnant and lactating mothers.
4. Major depressive disorder with psychotic symptoms.
5. Not available for follow-up

A comprehensive medical history was obtained, encompassing details of comorbidities, allergies, past hospital admissions, reproductive history, and addictions.A total of n=80 patients were diagnosed with mild to moderate (Stage I and Stage II hypertension as per JNC 8 criteria were included). A thorough general physical examination and systemic assessment were conducted. Blood pressure (BP) was measured according to standard protocol after a 5-minute rest in the normal upright position, using a mercury sphygmomanometer. Laboratory investigations including hemoglobin (Hb), total count (TC), differential count (DC), erythrocyte sedimentation rate (ESR), liver function tests (LFT), renal function tests (RFT), and electrocardiogram (ECG) were performed.Patients in Group I received a daily dose of Amlodipine 5mg, whereas those in Group II received Cilnidipine 10mg once daily, 30 minutes after breakfast, for 8 weeks. Participants were prohibited from using any other medications during the study period. Each patient underwent three visits: a baseline visit (Visit 0) on recruitment day, visit 1 after 30 days of medication, and Visit 2 after 60 days of treatment. Systolic and diastolic blood pressures, as well as heart rate, were measured at each visit. Clinical and laboratory parameters were reassessed at the end of the 8 weeks.Following the study, patients were advised to consult their physicians for further management. Drug efficacy was evaluated by manual sphygmomanometer measurements of blood pressure. Patient compliance was assessed using the pill count method at each visit, and adverse drug reactions were monitored through periodic phone calls and at every visit.

Statistical analysis: all the available data was refined and uploaded to an MS Excel spreadsheet and analyzed by SPSS version 21 on the Windows platform. The continuous variables were represented as mean, standard deviations, and percentages. The categorical variables were calculated using a chi-square test for differences between two groups and p values of (<0.05) were considered significant.

Results

A total of n=80 cases were selected based on the inclusion and exclusion criteria and divided into two groups of n=40 each. Table 1 presents the demographic characteristics of participants in a study comparing the effects of two medications for mild and moderate hypertension: Amlodipine (Group I) and Cilnidipine (Group II). Each group has 40 participants.Age: The average age is similar between both groups; Group I has a mean age of 45.51 years (SD ± 2.67) and Group II has a mean age of 46.37 years (SD ± 3.25). The p-value (0.891) indicates no statistically significant difference in age between the groups.Weight: The average weight is also similar between the groups; with Group I having a mean weight of 70.64 kg (SD ± 8.21) and Group II having a mean weight of 69.19 kg (SD ± 7.66). The p-value (0.437) suggests no significant difference in weight between the groups.Height: Similar to other parameters, the average height is comparable between the groups. Group I has a mean height of 165.22 cm (SD ± 5.57) and Group II has a mean height of 166.24 cm (SD ± 9.94). The p-value (0.276) implies no statistically significant difference in height.Gender:

The distribution of male and female participants is slightly imbalanced, with both groups having more males than females. Group I has 27 males and 13 females, while Group II has 25 males and 15 females. However, the table doesn't provide a statistical test to assess the significance of this difference.

Table 1: Showing the Demographic profile of mild and moderate hypertension cases included in the study

Parameters	*Group I (Mean ± SD)*	*Group II (Mean ± SD)*	*P value*
Age in years	45.51 ± 2.67	46.37 ± 3.25	0.891
Weight (Kg)	70.64 ± 8.21	69.19 ± 7.66	0.437
Height in cms	165.22 ± 5.57	166.24 ± 9.94	0.276
Male/Female	27/13	25/15	0.674

Table 2 presents the mean Systolic Blood Pressure (SBP) readings in mmHg, recorded at different time intervals, for participants in two groups of a medication comparison study. Group I received Amlodipine (n=40), and Group II received Cilnidipine (n=40).*Baseline (Initial Visit)*: Both groups had similar average SBP at the beginning of the study (around 140 mmHg). The p-value (0.916) indicates no statistically significant difference in baseline SBP between the groups.*Visit 1 (30 days)*: Compared to baseline, both groups showed a significant decrease in SBP. Group, I had an average SBP of 124.69 mmHg (p-value = 0.021), while Group II had an average of 121.22 mmHg (p-value = 0.021). Both groups achieved statistically significant reductions in SBP compared to baseline.*Visit 2 (60 days):* Compared to baseline, both groups continued to maintain lower SBP levels. Group I had an average SBP of 121.31 mmHg (p-value = 0.016), and Group II had an average of 119.67 mmHg (p-value = 0.016). Again, both groups showed statistically significant reductions in SBP compared to baseline.

Table 2: showing the mean parameters of Systolic Blood Pressure (SBP) in mmHg recorded at various intervals in the cases of the study

Parameters	*Group I (Mean ± SD)*	*Group II (Mean ± SD)*	*P value*
Initial visit (baseline)	140.34 ± 2.64	141.72 ± 3.0	0.916
Visit 1 (30 days after medication)	124.69 ± 2.11	121.22 ± 2.04	0.021
Visit 2 (60 days after medication)	121.31 ± 1.67	119.67 ± 1.92	0.016

Table 3 presents the mean Diastolic Blood Pressure (DBP) readings in mmHg, recorded at different time intervals.*Baseline (Initial Visit):* Both groups had similar average DBP at the beginning of the study (around 91 mmHg). The p-value (0.720) indicates no statistically significant difference in baseline DBP between the groups.*Over time: Visit 1 (30 days):* Compared to baseline, both groups showed a significant decrease in DBP. Group I had an average DBP of 86.34 mmHg (p-value = 0.02), while Group II had an average of 84.33 mmHg (p-value = 0.02). Both groups achieved statistically significant reductions in DBP compared to baseline.*Visit 2 (60 days):* Compared to baseline, both groups continued to maintain lower DBP levels. Group I had an average DBP of 81.04 mmHg (p-value = 0.01), and Group II had an average of 80.19 mmHg (p-value = 0.01). Again, both groups showed statistically significant reductions in DBP compared to baseline.Both Amlodipine and Cilnidipine effectively reduced DBP in participants with mild or moderate hypertension over

60 days. While Group II (Cilnidipine) had a slightly lower average DBP at all measured points.

Table 3: showing the mean parameters of Diastolic Blood Pressure (DBP) in mmHg recorded at various intervals in the cases of the study

Parameters	*Group I (Mean ± SD)*	*Group II (Mean ± SD)*	*P value*
Initial visit (baseline)	91.25 ± 2.15	90.91 ± 1.37	0.720
Visit 1 (30 days after medication)	86.34 ± 1.91	84.33 ± 1.60	0.021
Visit 2 (60 days after medication)	81.04 ± 1.64	80.19 ± 1.33	0.013

Baseline (Initial Visit): Both groups had similar average heart rates at the beginning of the study (around 79 beats per minute). The p-value (0.152) indicates no statistically significant difference in baseline heart rate between the groups.*Heart Rate Changes over Time: Visit 1 (30 days):* Compared to baseline, both groups showed a significant decrease in heart rate. Group I had an average heart rate of 75.15 beats per minute (p-value = 0.02), while Group II had an average of 73.67 beats per minute (p-value = 0.02). Both groups achieved statistically significant reductions in heart rate compared to baseline.*Visit 2 (60 days):* Compared to baseline, both groups maintained lower heart rates. Group I had an average heart rate of 73.02 beats per minute (p-value = 0.01), and Group II had an average of 69.22 beats per minute (p-value = 0.01). Again, both groups showed statistically significant reductions in heart rate compared to baseline.At all measured time points, Group II (Cilnidipine) had a slightly lower average heart rate compared to Group I (Amlodipine).

Table 4: showing the mean heart rate (beats per minute) recorded at various intervals in the cases of the study

Parameters	*Group I (Mean ± SD)*	*Group II (Mean ± SD)*	*P value*
Initial visit (baseline)	78.92 ± 5.67	79.27 ± 8.16	0.152
Visit 1 (30 days after medication)	75.15 ± 4.92	73.67 ± 6.64	0.02
Visit 2 (60 days after medication)	73.02 ± 3.21	69.22 ± 2.97	0.01

Figure 1 shows the reported adverse events experienced by participants in two groups of a medication comparison study during two months. Group I received Amlodipine (n=40), and Group II received Cilnidipine (n=40).*Number of adverse events: At one month:* More participants in Group I (35%) reported adverse events compared to Group II (30%).*At two months:* Group I maintained a higher number of reported events (25%) compared to a significant decrease in Group II (10%).

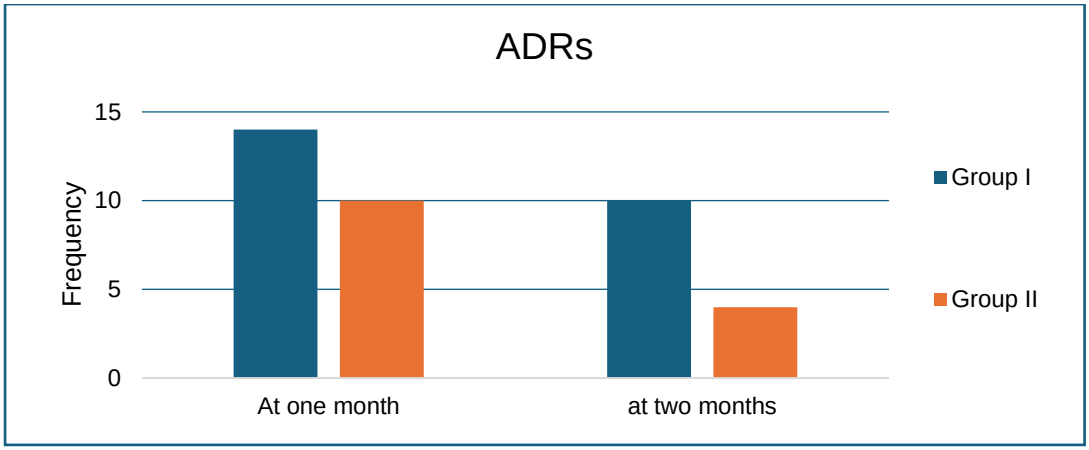

Figure 1: Showing the frequency of Adverse Drug reactions reported in the cases of the study

Table 5 provides a more detailed breakdown of the mild/moderate adverse events (ADRs) reported by participants in two groups of a medication comparison study. Data is presented for both one month and two months after starting medication.*At One Month:Frequency of ADRs:* Both groups reported similar frequencies of ADRs: 14 (35.0%) in Group I and 12 (30.0%) in Group II.*Types of ADRs: Most common:* Fatigue, muscle pain, headache, and headache with gastrointestinal (GI) upset were the most frequently reported events in both groups.*Variations:* Group I had a slightly higher prevalence of "headache + GI upset" and "vomiting" compared to Group II.*At Two Months:Frequency of ADRs:* Group I again reported a higher number of ADRs (10, 25.0%) compared to Group II (4, 10.0%).*Types of ADRs: Most common:* Similar to one month, headache and fatigue were the most frequently reported events, followed by ankle edema (present only in Group I).Compared to one month, the prevalence of most ADRs decreased in both groups, except for ankle edema which was newly reported in Group I.This table suggests that both Amlodipine (Group I) and Cilnidipine (Group II) can cause mild/moderate adverse events in some individuals. While Group I seemed to have a higher frequency and wider range of reported ADRs. None of the patients were dropped from the medication due to these adverse effects because all the adverse effects were mild and did not requiretaking off the medication.

Table 5: Details of mild/ moderate adverse effects reported in the cases of the study

ADRs at one month	*Group I*	*Group II*
Fatigue	5(12.5%)	4(10.0%)
Muscle pain	2(5.0%)	3(7.5%)
Headache	2(5.0%)	3(7.5%)
Headache + GI upset	3(7.5%)	1(2.5%)
Abdominal pain	1(2.5%)	1(2.5%)
Vomiting	1(2.5%)	0(0.00%)
Total	14(35.0%)	12(30.0%)
ADRs at Two months		
Headache	2(5.0%)	1(2.5%)
Fatigue	3(7.5%)	1(2.5%)
Abdominal pain	1(2.5%)	0(0.00%)
Ankle edema	4(10.0%)	2(5.0%)
Total	10(25.0%)	4(10.0%)

Discussion

Hypertension presents a significant concern among patients, contributing to various health-related complications. As both systolic and diastolic blood pressure levels increase, the risk of cardiovascular morbidity and mortality escalates. The current study aims to evaluate the impact of Amlodipine 5 mg once daily and Cilnidipine 10 mg once daily in hypertensive patients.Calcium channel blockers are commonly employed in our hospital setting for hypertension management. They function by inhibiting calcium influx into vascular smooth muscle cells, thereby inducing relaxation and vasodilation, consequently leading to a decrease in blood pressure [11]. The clinical efficacy of dihydropyridine calcium channel blockers primarily stems from their action on L-type calcium channels, predominantly found in arterioles [12].Despite their comparable efficacy in blood pressure control, the incidence of pedal edema varies among calcium channel blockers, likely attributable to differences in their effects on peripheral arteries [13]. Drugs specifically targeting L-type calcium channels reduce blood pressure by dilating resistance arterioles, which may result in increased pressure in the afferent capillaries and subsequent extravasation. Notably, combining an L-type calcium channel blocker with an angiotensin-converting enzyme inhibitor has been observed to reduce the incidence of pedal edema [14].N-type calcium channels, distributed in neurons, play a role in regulating sympathetic activity [15]. Given that venules are innervated by sympathetic neurons, N-type calcium channel blockers induce vasodilation [16].Cilnidipine boasts a prolonged duration of action and can be conveniently administered once daily [17]. Clinical studies conducted by Nagahama et al. [18] and Limura et al. [19] demonstrated the antihypertensive efficacy of cilnidipine. Hoshide et al. reported a significant reduction in heart rate among hypertensive patients treated with cilnidipine compared to amlodipine [20] similar observations were found in this study where the reduction in heart rates was significant.

In this study, we found both amlodipine and cilnidipine groups exhibited decreased peripheral blood pressure after two months of treatment. The mean decrease in SBP was 19.31 mmHg in the Amlodipine group similarly, the mean decrease of SBP in the cilnidipine group was 22.05 mmHg. Diastolic blood pressure decreased by 10.21 and 10.72 mmHg in group I and group II respectively. Both medications significantly reduced Systolic and Diastolic Blood Pressure (SBP and DBP) and heart rate in both groups over 60 days. Both medications effectively reduced heart rate in both groups over 60 days. Group II (Cilnidipine) had a slightly lower average heart rate at all measured points, but the difference wasn't statistically significant.The results of this study are in concordance with observations of S Morimoto et al. [21] reported that amlodipine 5 mg and cilnidipine 10 mg are equally effective in controlling blood pressure in patients with mild to moderate essential hypertension. Similarly, R Mohan et al. [22] investigated the effect of amlodipine and cilnidipine on hemodynamic and vascular indices, concluding that both drugs were equally effective in blood pressure control, but cilnidipine showed improvements in central hemodynamic and vascular indices such as pulse wave velocity, arterial stiffness, and central aortic pressure. In this study examination of adverse effects revealed both groups reported mild/moderate adverse drug reactions. Group I consistently reported a higher number of events compared to Group II Fatigue and headache were the most commonly reported events in both groups. Group I also experienced a wider range of events, including headache + GI upset and vomiting at one month and ankle edema at two months. In a study by R Shetty et al. [23] patients with amlodipine-induced pedal edema were switched to cilnidipine, resulting in the resolution of edema within four weeks. There were no significant changes in mean arterial pressure or heart rate, suggesting equivalent efficacy between amlodipine and

cilnidipine.Xu GLet al. [24] demonstrated that cilnidipine is well tolerated by hypertensive patients, with minimal adverse events such as headache, dizziness, cough, and gastrointestinal disturbances, which are comparable to those associated with amlodipine.Therefore, calcium channel blockers that act on N-type calcium channels (cilnidipine) have the potential to dilate venules through the sympathetic system, thereby reducing the incidence of pedal edema compared to blockers that solely target L-type calcium channels. These findings align closely with the results of my study where we did not find the incidence of pedal edema in the cilnidipine group. Uneyama et al. [25] illustrated that even at submicromolar concentrations, cilnidipine effectively inhibits N-type calcium channels in isolated sympathetic neurons.Nagai H. et al. [26] showcased the cardioprotective potential of cilnidipine in a rabbit model of myocardial infarction. Their findings indicated that cilnidipine reduced myocardial interstitial norepinephrine levels during ischemia and reperfusion, leading to a decrease in infarct size and ventricular premature beats. Incidences of morning hypertension and white-coat hypertension, which are closely linked to sympathetic activity, have been clinically shown to be effectively managed with cilnidipine [27].Our study's robustness lies in its randomization process, ensuring unbiased allocation of subjects. We maintained frequent blood pressure monitoring with high patient compliance throughout the study. Additionally, our research is conducted without any conflicts of interest.

Conclusion

In conclusion, both the calcium channel blockers amlodipine and cilnidipine exhibit equivalent efficacy in reducing systolic and diastolic blood pressure in patients with mild to moderate essential hypertension. Cilnidipine, as a fourth-generation calcium channel blocker, offers a promising pharmacological profile. In addition to its blood pressure-lowering effects, cilnidipine demonstrates notable safety and provides additional benefits including renoprotective, cardioprotective, and neuroprotective effects. Its dual action on both L and N-type calcium channels, preventing pedal edema, sets it apart from amlodipine, which solely targets L-type calcium channels. Moreover, cilnidipine does not induce reflex tachycardia due to its dual blockade of both L and N-type calcium channels.

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