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Original Research Article

Comparison of Antihypertensive Efficacy of Amlodipine and Cilnidipine as an add-on drug to Baseline medication in Hypertensive Chronic Kidney Disease patients

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ABSTRACT

INTRODUCTION: The prevalence of chronic kidney disease (CKD) is high in India, with hypertension being a significant contributing factor. The current CKD management guidelines underscore the importance of tight blood pressure control. Cilnidipine, a novel Calcium Channel Blocker (CCB), shows promise due to its unique mechanism of blocking both L and N-type calcium channels, resulting in improved efficacy and fewer adverse effects compared to traditional CCBs like amlodipine.

OBJECTIVES: This study aims to compare the effectiveness of amlodipine and cilnidipine as add-on treatments alongside baseline medications in reducing hypertension.

METHODS: A year-long prospective observational study was conducted at Government T.D. Medical College, Alappuzha, from January 2016 to December 2016. The study involved 90 hypertensive CKD patients, with 45 patients receiving amlodipine and 45 patients receiving cilnidipine in conjunction with their baseline medications. Eligible participants were aged 18-80, with a glomerular filtration rate (GFR) between 30-60 ml/min and blood pressure exceeding 140/90 mmHg despite specific medications for at least one month. Standardized measurements of systolic and diastolic blood pressure were taken, and mean values were analysed.

RESULTS: Both amlodipine and cilnidipine led to significant reductions in systolic and diastolic blood pressure. While there was no statistically significant difference in mean reduction of systolic blood pressure between the two treatment groups, cilnidipine demonstrated a notably superior reduction in mean diastolic blood pressure compared to amlodipine.

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CONCLUSION: Cilnidipine's ability to block both L and N-type calcium channels resulted in a greater reduction in mean diastolic blood pressure compared to amlodipine. This suggests cilnidipine's potential as a preferable alternative for managing hypertension in CKD patients.

KEYWORDS: Hypertension, Chronic Kidney Disease, Systolic and diastolic blood pressure, Cilnidipine, Amlodipine

INTRODUCTION

Chronic Kidney Disease (CKD) is characterized by a gradual deterioration in renal function extending over a span of at least 3 months. The Kidney Disease Outcomes Quality Initiative (KDOQI) outlines CKD as a condition marked by a glomerular filtration rate (GFR) that falls below 60 mL/min/1.73 m2 for a duration of 3 months or more.[1] Elements linked to the advancement of kidney disease among CKD patients encompass conditions like diabetes mellitus, hypertension, and hyperuricemia. Of these factors, hypertension stands out as a prominent contributor to CKD's progression. The current guidelines for managing CKD strongly advocate for meticulous regulation of hypertension through suitable antihypertensive medications.[2]

Hypertension stands as the most prevalent risk factor in the emergence of cardiovascular disease. Approximately one billion individuals across the world are grappling with hypertension.[3] The occurrence of hypertension seems to fluctuate among diverse racial and ethnic groups. [4,5] In the Indian population, the recorded prevalence of hypertension is documented at 29.8%.[6] Findings from the Framingham Heart Study have unveiled that individuals with normal blood pressure at the age of 55 face a 90% probability of developing hypertension over their lifetime.[7] As per the directives of the Joint National Commission (JNC-8), hypertension is categorized as follows: Normal when the Systolic Blood Pressure (SBP) is below 120 mmHg and the Diastolic Blood Pressure (DBP) is below 80 mmHg; Pre-Hypertension with SBP ranging from 120-139 mmHg and DBP from 80-89 mmHg; Stage 1 when SBP falls between 140-159 mmHg and DBP between 90-99 mmHg; and Stage 2 when SBP is equal to or surpasses 160 mmHg and DBP is equal to or surpasses 100 mmHg.[8]

In accordance with the recommendations put forth by the European Society of Hypertension and European Society of Cardiology, all significant categories of antihypertensive medications [including Diuretics, β-blockers, Calcium Channel Blockers (CCBs), Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)] are deemed suitable for both initial treatment and ongoing management, whether administered alone or in combination.[9] While ACEIs and ARBs are preferred during the initial phases of therapy, it's important to highlight that their simultaneous use with CCBs demonstrates a synergistic impact, enhancing not only the effectiveness of antihypertensive action but also providing added kidney protection (renoprotection).[10]

Currently, fourth-generation CCBs such as cilnidipine possess the unique ability to inhibit both types of calcium channels, resulting in distinct effects that go beyond the typical outcomes of their class. These effects encompass influences on heart rate and the renin-

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aldosterone system. These particular effects are considered advantageous due to their capacity to confer organ protection alongside the management of hypertension. [11]

This research aims to compare the antihypertensive effects of cilnidipine and amlodipine as an add-on medication to baseline therapy in patients with CKD.

MATERIALS AND METHODS

This prospective observational study was carried out in the Department of Nephrology at Government T.D. Medical College, Alappuzha, spanning a year from January 2016 to December 2016. The research involved 90 hypertensive patients with chronic kidney disease (CKD), with 45 individuals receiving cilnidipine and the rest 45 receiving amlodipine, both in addition to their baseline medications.

The study encompassed CKD patients aged between 18 and 80 years, with a Glomerular Filtration Rate (GFR) ranging from 30 to 60 ml/min, and exhibiting blood pressure readings above 140/90 mmHg despite being on loop diuretics (Tab. Frusemide 80 mg BD), α-blockers (Tab. Prazosin 10 mg BD), and β-blockers (Tab. Metoprolol 50 mg BD) for at least a month. Exclusions encompassed individuals utilizing alternative medical systems, pregnant women, and those facing hypertensive or cardiac emergencies. Ethical approvals were secured from the Institutional Ethics Committee (IEC No. B6/79/2015/TDMCA dated 02/12/2015) and the Institutional Research Committee (IRC) before the study initiation. Stringent confidentiality measures were upheld throughout the study.

The investigation took place over a year in the Nephrology Outpatient Department (OPD). Participants provided informed written consent. Blood pressure measurements were taken under standardized conditions, with systolic and diastolic readings recorded twice, 20 minutes apart, and the mean value was used for analysis. Patient weight (in kilograms) was assessed using digital platform weighing scales. Individuals receiving either amlodipine 5 mg BD or cilnidipine 10 mg BD as add-on therapy were included. Regular follow-ups occurred every two months for six months, with blood pressure measurements documented during each visit. If blood pressure remained above 140/90 mmHg, amlodipine and cilnidipine dosages were increased to 10 mg BD and 20 mg BD, respectively. Data entry utilized Excel 2010 and analysis was performed using SPSS 18.

Quantitative continuous variables were presented as Mean ± Standard deviation. Changes in blood pressure within the same group before and after antihypertensive medication were assessed using a paired t-test. Additionally, variations in blood pressure change between the amlodipine and cilnidipine groups at each visit were analysed through an unpaired t-test. Statistical significance was set at a p-value below 0.05.

RESULTS

A total of 90 hypertensive CKD patients were included in the study - 45 patients received cilnidipine and 45 patients received amlodipine along with the baseline medications. There were 61 (67.8%) males and 29 (32.2%) females. Out of 61 males, 29 (32.2%) were

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treated with amlodipine and 32 (35.6%) were treated with cilnidipine. Out of 29 females, 16 (17.8%) were treated with amlodipine and 13 (14.4%) were treated with cilnidipine.

The Mean ± SD of SBP and DBP in both amlodipine and cilnidipine groups before and after treatment at fourth visit are as given in Table 1.

Table 1: The Mean ± SD of SBP and DBP under study

Parameter	Amlodipine		Paired t test (t, p)	Cilnidipine		Paired t test (t, p)
	Before Treatment	After Treatment		Before Treatment	After Treatment	
SBP	158.4±10.9	140.6±5.5	14.72, <0.001	161.9±15.2	138.4±7.4	9.55, <0.001
DBP	96.4±6.07	86.04±2.4	11.48, <0.001	96.3±6.3	82.3±5.7	15.09, <0.001

Systolic Blood Pressure (SBP)-

Students paired t-test before and after study (at fourth visit) in both amlodipine and cilnidipine groups showed that there is a significant reduction in mean SBP in both groups as shown in table 1.

The comparative evaluation of efficacy of reduction in mean SBP over time of amlodipine with cilnidipine group at each visit (Table 2) showed that there is no statistically significant difference in reduction of mean SBP between the two treatment groups at each visit.

Table 2: Comparative evaluation of efficacy of mean SBP of amlodipine with cilnidipine at each visit

Mean SBP	Amlodipine	Cilnidipine	t-value	p-value	Significance
Visit 1	158.4±10.9	161.9±15.2	-1.226	0.224	Not Significant
Visit 2	151.2±11.3	151.3±11	-0.075	0.94	Not Significant
Visit 3	146.3±8.2	145.3±8.7	0.525	0.601	Not Significant
Visit 4	140.6±5.5	138.4±7.4	1.589	0.116	Not Significant

Thus, it is found that in both amlodipine and cilnidipine groups, the SBP before and after study is found to be statistically significant but when the SBP at each visit is compared between the groups, it is not found to be statistically significant.

The slope of the line chart is a visible indicator of the efficacy of the drug. It can be clearly seen that the slope of cilnidipine graph is close to that of amlodipine indicating that the overall efficacy of cilnidipine in reducing mean SBP is comparable to that of amlodipine. But still the minor increase in the slope of cilnidipine graph indicates the minor superiority of cilnidipine over amlodipine in reducing mean SBP but it is not statistically significant as is proved by the T- test.

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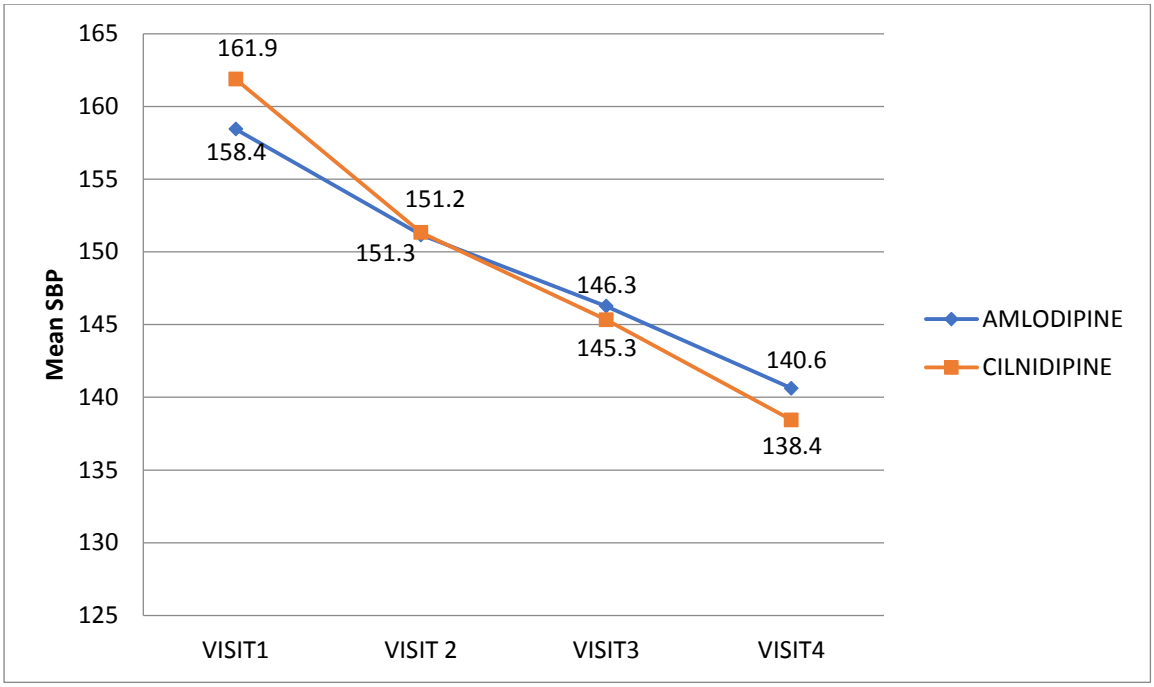

Figure 1: Line chart of mean SBP over time.

Diastolic Blood Pressure (DBP)-

Using the paired t test, it was found that the DBP in both the amlodipine and cilnidipine groups showed significant statistical difference after study when compared to before study. Hence, it is seen that both amlodipine and cilnidipine reduces DBP significantly after study when compared to before study, shown in Table 1.

Comparison of mean DBP between the amlodipine and cilnidipine groups using unpaired t- test showed statistical significance in all the visits except the first. Hence, it is found that, in comparison to amlodipine, cilnidipine reduces DBP significantly as time passes or in other words, cilnidipine has better therapeutic efficacy in lowering DBP when compared to amlodipine as shown in table 3.

Table 3: Comparative evaluation of efficacy of mean DBP of amlodipine with cilnidipine at each visit

Mean DBP	Amlodipine	Cilnidipine	t-value	p-value	Significance
Visit 1	96.4±6.1	96.3± 6.3	0.07	0.946	Not Significant
Visit 2	92.8±5.6	88.4±8.5	2.9	0.006	Significant
Visit 3	89.3±3.5	85.2±6.9	3.6	<0.001	Significant
Visit 4	86.0±2.4	82.3±5.7	4.1	<0.001	Significant

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The slope of the line chart of mean DBP (Figure 2) showed that cilnidipine has a higher slope than that of amlodipine and so is the higher efficacy of cilnidipine in reducing DBP when compared to that of amlodipine.

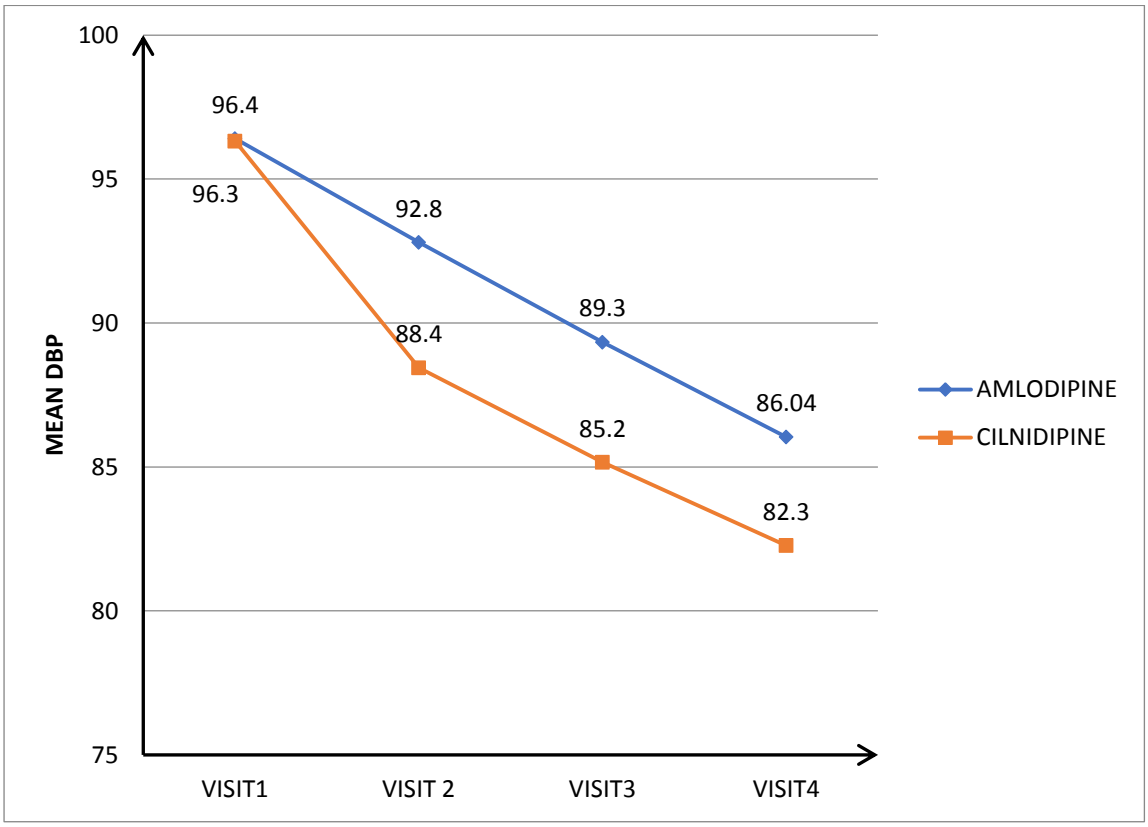

Figure 2: Line chart of mean DBP over time

DISCUSSION

In this study, 63.3% of the patients under study had stage 2 hypertension whereas 36.7% had stage 1 hypertension. The mean SBP in the amlodipine group before and after treatment were 158.4 ±10.9 and 140.6 ±5.5 respectively whereas that in cilnidipine was 161.8 ±15.2 and 138.4 ±7.37 respectively. The mean DBP in the amlodipine group before and after treatment were 96.4 ±6.07 and 86.0 ±2.4 respectively whereas that in the cilnidipine group were 96.3 ±6.3 and 82.2 ±5.6 respectively. The mean systolic and diastolic BP in both the amlodipine and cilnidipine groups when compared before and after study using the paired t test were found significant with a p-value less than 0.01%. The SBP after study when compared between the groups using unpaired t-test was found to be statistically not significant whereas the mean DBP after treatment when compared between the groups using unpaired t-test was found to be significant with p-value of 0.01% and t-value of 4.1. Therefore, cilnidipine has been found to be more efficacious than amlodipine in lowering DBP.

In the study by Zaman et al, the mean SBP before and after study in the amlodipine group was 166 ±16 and 152 ±11 respectively with a p-value less than 0.001. The SBP before and after study in the cilnidipine group were 166 ± 11 and 154 ± 11 respectively with a p-

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value less than 0.001. The mean DBP in the amlodipine group before and after treatment where 98 ± 8.6 and 90 ±7.8 respectively with a p-value less than 0.001 whereas in the cilnidipine group were 100 ±10 and 92 ± 6.8 respectively with a p-value less than 0.001.[12]

According to study by Adake et al, both amlodipine and cilnidipine have equal efficacy in reducing BP in hypertensive individuals. However, there was no significant difference in the antihypertensive efficacy of both drugs ($p > 0.05$).[13]

In a study by K. Ananda Babu, non-significant results were obtained while comparing the mean SBP and DBP among the two groups. The mean SBP in the amlodipine group patients was 139.1 and that in the cilnidipine group patients was 144.2 mm of Hg respectively. The mean DBP in the amlodipine and cilnidipine group patients was 80.2 and 85.3 mm of Hg respectively. Both amlodipine and cilnidipine showed equal efficacy in controlling the BP of the patients ($p < 0.05$).[14]

The study's constraints include its relatively modest sample size and the limited duration of observation. Furthermore, the study's design was that of a prospective observational study. To achieve a more robust assessment of efficacy, a randomized controlled trial would be more ideal. Additionally, the administration of medications took place within patients' own homes and not under direct supervision. Consequently, the complete adherence of patients to their prescribed medication regimen cannot be definitively verified and the study hinges on the assumption that participants remained consistent in their medication intake.

CONCLUSION

In this study both amlodipine and cilnidipine significantly reduced the mean BP but cilnidipine was found to be superior to amlodipine in reducing the mean DBP and equally efficacious in reducing SBP.

CONFLICT OF INTEREST: None

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