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Original Research Article

Comparative Study on the Effects of Amlodipine and Cilnidipine on Heart Rate and Proteinuria in Subjects with Hypertension with Proteinuria: A Randomized Open-Label Trial

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Conflict of interest: Nil

Abstract:

Background: Drugs in the calcium channel blocker (CCB) class are frequently used to treat hypertension. Because of its dual L/N-type CCB characteristic, cilnidipine is a unique CCB that favours extra protection for the heart and kidneys. The purpose of this study was to assess the effects of amlodipine and cilnidipine on heart rate and proteinuria in hypertensive patients, as well as their linearity over time.

Methods: Patients attending the General Medicine OPD at JLNMCH, Bhagalpur, Bihar, who were hypertensive and had proteinuria were the subjects of a prospective, randomized, open-label study conducted in the Department of Pharmacology. The study included 60 participants who met the inclusion and exclusion criteria. In addition to weekly heart rate monitoring, baseline and 12-week measurements were made of heart rate and the urine protein-to-creatinine ratio (UPCR). Amlodipine and cilnidipine dosages were adjusted based on blood pressure regulation. The findings were analyzed using repeated measure ANOVA, Cramer's V-test, independent sample t-test, and descriptive statistics.

Results: Both groups' demographic profiles matched rather well. Subjects receiving amlodipine had a considerably greater heart rate at 12 weeks, but those receiving cilnidipine had a significantly higher heart rate from baseline ($P < 0.05$). Additionally, there was a substantial intergroup difference ($P < 0.05$) between the cilnidipine and amlodipine groups, with the former showing a large increase in UPCR and the latter a significant decrease.

Conclusion: Because of its cardio protective and renoprotective properties, cilnidipine is therefore a preferable option for hypertensive individuals with proteinuria.

Keywords: Proteinuria, Heart Rate, Amlodipine, Cilnidipine.

Introduction

Given its role in early mortality in both industrialized and developing nations, hypertension (HTN) is a significant public health concern.[1] Coronary heart disease, congestive heart failure (CHF), stroke, renal impairment, and peripheral vascular disease are among the consequences of chronic hypertension.[2,3] Therefore, the cornerstone of treating hypertension patients to avoid cerebrovascular and cardiovascular consequences is early detection and management.[4] Thanks to advancements in the detection and treatment of hypertension and associated sequelae, there has been a notable decrease in the death rate from both cerebrovascular and cardiovascular problems in recent years.[5]Proteinuria is the first sign of hypertensive nephropathy, and it increases the risk of cardiovascular problems and further compromises renal function.[3] The development of chronic kidney disease (CKD) is accelerated by chronic and uncontrolled hypertension (HTN), underscoring the significance of optimal blood pressure (BP) control in maintaining renal function and, consequently, lowering morbidity and mortality from cardiovascular complications.[6]When it comes to treating hypertension, calcium channel blockers (CCBs) are a significant family of medications that are often utilized as first-line treatments regardless of the patient's age, gender, race, or other concomitant illnesses. The only exception to this rule are individuals who also have renal illness, as they have

been shown to benefit more overall from renin-angiotensin system (RAS) blocking medications.[7,8] However, CCBs have an extra benefit over ACE inhibitors and angiotensin receptor blockers (ARBs) in that they can also considerably lower blood pressure as dosage is increased.[9] Amlodipine is an L-type CCB that offers the best blood pressure control over a 24-hour period to patients with HTN. Its efficacy and safety have been demonstrated.[4] The reflex rise in heart rate brought on by the hypotensive impact of amlodipine is, nevertheless, a significant side effect.[5] Furthermore, it's unclear if amlodipine has any notable renoprotective effects.[10]

Another dihydropyridine calcium channel blocker (CCB) that blocks both L- and N-type calcium channels is cilnidipine.[11] A few studies have indicated that the extra N-type CCB characteristic may aid to protect the kidneys in addition to suppressing the reflex increase in heart rate.[7,12]

Therefore, the aim of the current study was to assess how amlodipine and cilnidipine affected heart rate and proteinuria in hypertensive participants, as well as how linearly these effects occurred with time.

Material and Methods

This open-label, randomized, parallel group study was carried out in the Department of Pharmacology at Jawaharlal Nehru Medical College and Hospital in Bhagalpur, Bihar, in conjunction with the Medicine Department. Patients with hypertension and proteinuria who visit the JLNMCH General Medicine Department from February 2023 to January 2024.

The sample design was a purposive sampling technique.

The sample size was determined to be 15 and 53 for 4% and 16% prevalence, respectively, using an estimating technique with the following parameters: effect size of 10%, level of significance of 5%, and prevalence of hypertensive participants with proteinuria ranging from 4% to 16%. We chose to use 60 subjects, divided into two groups of thirty each.

This study included a selection of male and female patients who were at least 40 years old, had coexisting proteinuria, were hypertensive (grade I and II), and gave their informed consent. Exclusions from this study included patients with end-stage renal disease, CHF, heart block, aortic stenosis, systolic blood pressure (SBP) ≥ 180 mmHg and/or diastolic blood pressure (DBP) ≥ 110 mmHg before or during the washout period, normotensive subjects with proteinuria, hypertensive subjects on two or more antihypertensive medications, pregnant and lactating women, and those who had taken amlodipine, celinadipine, ACE inhibitors, or an ARB within 30 days prior to enrollment.

A thorough medical history was obtained, and an examination was performed. Investigations that were necessary were blood urea nitrogen, serum creatinine, echocardiography, blood pressure, urine routine, and ECG.

Cramer's V-test and descriptive statistics were employed to examine the demographic factors. Measurement repeated the variation in each parameter from the beginning to the end of the 12-week period was examined using an ANOVA.

To compare groups, the independent sample t-test was employed. R software and Microsoft Excel sheets were used to examine all of the data. A value of $P < 0.05$ was deemed statistically significant.

Results

The demographic factors, which are compiled in Table 1, did not significantly differ between the two groups.

Table 1: Demographic profile of subjects in amlodipine and cilnidipine groups

Characteristics	Group I (n=30)	Group II (n=30)
Age (mean ± SD)	63.27±8.55	63±6.28
Gender		
Male	17	16
Female	13	14
BMI		
Normal	22	24
Overweight	6	5
Obese	2	1
Socioeconomic status		
Upper middle class	00	01
Middle class	26	25
Lower middle class	04	04
Previous antihypertensive medication		
Thiazide/thiazide-like diuretic	18	20
Beta-blockers	12	10

Duration of hypertension (years)		
<10	3	1
10–20	22	28
>20	5	1

SD: Standard deviation

At the conclusion of the trial, the mean dosage of cilnidipine in Group II was 10 mg/day, whereas the mean dose of amlodipine in Group I was 5.2 ± 0.82 mg/day. There were 16 and 12 individuals with type 2 diabetes mellitus in Group I and Group II, respectively. Of these, ten were on metformin in each group, while the remaining diabetic participants were on a combination of metformin and glimepiride in the amlodipine group (6) and the cilnidipine group (2). At baseline, the mean heart rate of the patients in the cilnidipine group was substantially higher than that of the subjects in the amlodipine group ($P < 0.049$). Figure 1 shows the significant difference in mean heart rate from baseline at 3 weeks, 6 weeks, and 12 weeks for both the amlodipine and cilnidipine groups (ANOVA - $P < 0.001$). Nevertheless, following treatment with the study drugs, the intergroup difference in the change in mean heart rate from baseline was significant only at 6 and 12 weeks (independent sample t-test - $P < 0.01$), but not at 3 weeks (independent sample t-test - $P > 0.05$).

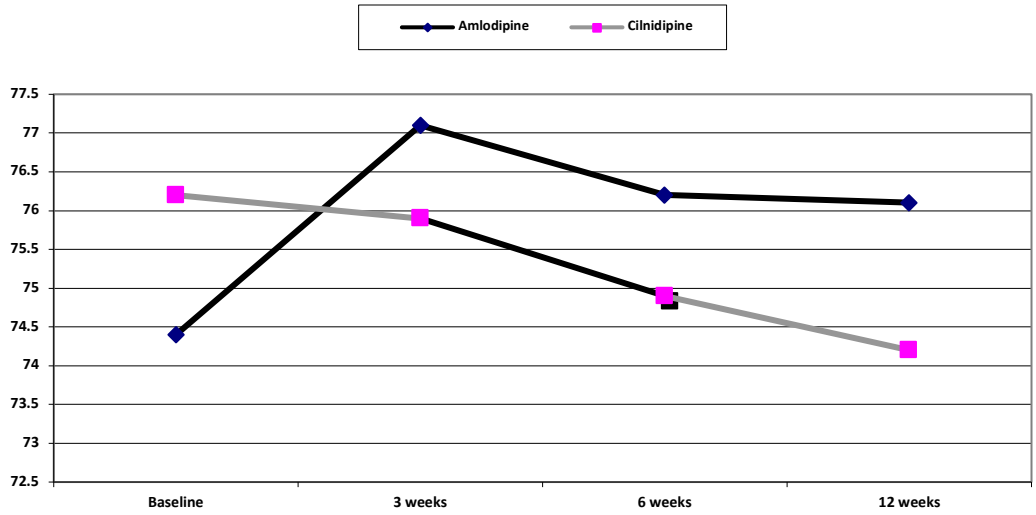

Figure 1: Mean heart rate in amlodipine group and cilnidipine group at specific intervals

Figure 2 shows that the mean UPCR increases in the amlodipine group and the mean UPCR decreases in the cilnidipine group are both statistically significant (independent sample t-test - $P < 0.001$). Additionally, at 12 weeks of treatment, the intergroup difference in the mean UPCR change from baseline was statistically significant (independent sample t-test - $P < 0.001$).

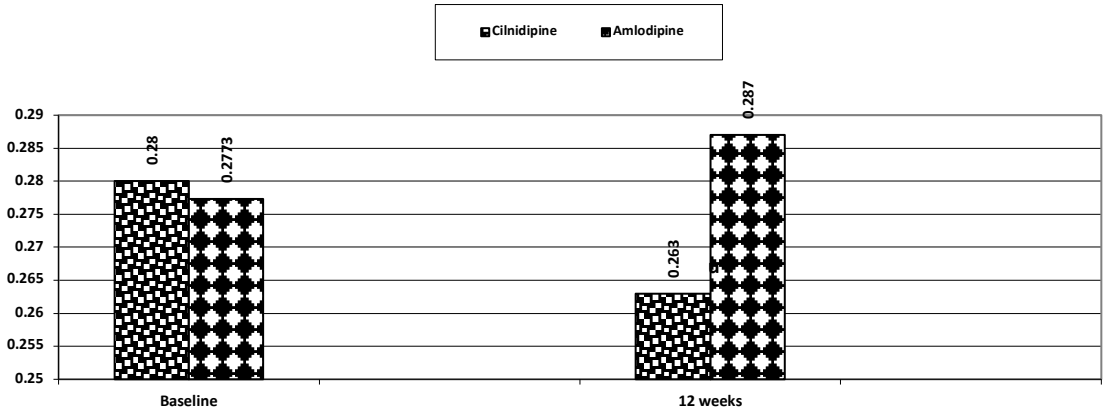

Figure 2:

Discussion

CCBs are an outstanding class of antihypertensive medications because of their ability to maintain normal blood pressure levels, hence minimizing cardiovascular and renal consequences of hypertension.[8] The current investigation set out to assess and contrast the renoprotective and cardiovascular effects of amlodipine and cilnidipine, two dihydropyridines known as CCBs. At the end of three weeks, six weeks, and twelve weeks, the mean heart rate of the individuals in the amlodipine group increased considerably from 74.73 ± 3.64 bpm at baseline to 77.17 ± 4 bpm.

Conversely, at the end of 3 weeks, 6 weeks, and 12 weeks, the mean heart rate of those receiving cilnidipine 10 mg/day decreased statistically significantly from baseline (76.63 ± 3.68 bpm) to 74.7 ± 3.55 bpm. After 12 weeks, the UPCR in the amlodipine group increased statistically significantly from 0.2773 ± 0.03 mg/mg at baseline to 0.2817 ± 0.04 mg/mg. Subjects in the cilnidipine group experienced a substantial reduction in UPCR from 0.28 ± 0.03 mg/mg at baseline to 0.24 ± 0.03 mg/mg at 12 weeks of treatment, in contrast to the amlodipine group. Additionally, at the conclusion of 6 and 12 weeks of treatment, there was an intergroup difference in the change in mean heart rate from baseline that was statistically significant. In a similar vein, there was a statistically significant difference between the amlodipine and cilnidipine groups in the change in mean UPCR values from baseline to 12 weeks.

In a study by Kaur et al.,[9] it was discovered that after 6 weeks, 30 participants who took amlodipine at a level of 5–10 mg/day had a noticeably faster pulse rate. Hoshide et al.[15] have also reported an increase in daytime pulse rate in 55 hypertensive persons taking amlodipine ≥2.5 mg/day. A comparable and statistically significant reduction in heart rate has been noted in a trial conducted by Manthri et al. with cilnidipine medication.[6] Cinnidipine treatment significantly reduced heart rate in 25 hypertensive people with type 2 diabetes mellitus, according to a Tanaka study [16]. Furthermore, a research by Hatta et al.[17] found that hypertensive patients with CKD receiving treatment with a RAS inhibitor experienced a substantial drop in heart rate with cilnidipine therapy.

Additionally, at 6 and 12 weeks, our study demonstrated a statistically significant difference in the mean heart rate change from baseline between the amlodipine and cilnidipine groups. These findings show a strong correlation with the findings of research by Hoshide et al., Kaur et al.,[18], Zaman and Kumari [9],[15]. According to 30.91%, 25.39%, 20.97%, and 22.30% of physicians, respectively, disregarding sympathetic overactivity in patients with high blood pressure can result in ischemic events, stroke, heart failure, and renal failure, increasing the morbidity and mortality of these patients. This study conducted by Dalvi et al.[19] also revealed these consequences. One possible explanation for the notable reduction in heart rate observed with cilnidipine therapy is the dual L/N-type CCB characteristic of the drug. Its sympatholytic function is explained by its inhibitory impact on N-type calcium channels, which reduces norepinephrine release from nerve terminals.[11] Cilinadipine inhibits heart sympathetic overactivity, whereas amlodipine exhibited less of the same inhibitory effect, according to a different study by Sakata et al.[12].

The findings of Kojima et al. [20] and Fujita et al. [21] are consistent with a statistically significant rise in proteinuria. Nevertheless, studies by Janssen et al. [23] and Jalal et al.[22] have not found any evidence of a substantial alteration in urine protein excretion or urinary albumin excretion rate in response to amlodipine medication. Such observed differences may be explained by coexisting diabetes mellitus in our study individuals and daily protein intake. A study by Hatta et al.[17] found that cilnidipine treatment significantly reduced proteinuria. Additionally, research by Manthri et al.[6] and Makawana and Panchal.[24] has demonstrated a noteworthy reduction in urine albumin excretion in hypertension patients receiving cilnidipine. Tsuchihashi et al. further investigation [25] revealed that while cilnidipine does not lessen proteinuria in individuals with renal hypertension, it does in essential HTN. Additionally, our study revealed a statistically significant difference in mean UPCR values between the amlodipine and cilnidipine groups from baseline to 12 weeks, which is consistent with research by Zaman and Kumari,[18] Abe et al.,[26] Uchida et al.,[27] Fujita et al.,[21], and Kojima et al.[20] In a study by Tanaka[16], the albumin-creatinine ratio significantly decreased in hypertensive patients with type 2 diabetes mellitus. This decrease was positively correlated with the change in heart rate, suggesting that cilnidipine's suppression of sympathetic activity may be the source of its renoprotective effects. Cilnidipine lowers glomerular pressure by blocking N-type calcium channels found in efferent arterioles and podocytes, which significantly protects podocytes and enhances the drug's antiproteinuric effects.[28]

Because the entire procedure was randomized, one of our study's strengths is that there was no bias in the assignment of participants to the amlodipine and cilnidipine groups. Our study is strengthened by the fact that the same researcher uses the same equipment to regularly check blood pressure and heart rate at weekly intervals. In both groups, there was complete adherence to the prescribed course of action, and no subjects were dropped or withdrew

for any reason. Another advantage of our study is that there were no conflicts of interest.

Still, there were several restrictions on our investigation. Initially, the study had a limited sample size and was open-label. Second, because HTN is a chronic illness, our study's 3-month evaluation period was extremely brief and necessitated a longer examination of the study's parameters.

Conclusion

Whereas cilnidipine dramatically lowers heart rate and proteinuria, amlodipine use is linked to reflex tachycardia and a marked rise in the rate of urine protein excretion, both of which have a negative impact on the prognosis of hypertensive patients. Therefore, because of its cardio protective and renoprotective properties, cilnidipine is a superior substitute for amlodipine in hypertensive individuals with proteinuria.

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