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RESEARCH ARTICLE

A randomized open-label study to compare the effects of amlodipine and cilnidipine on heart rate and proteinuria in subjects with hypertension with proteinuria

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ABSTRACT

Background: Calcium channel blockers (CCBs) are a commonly used class of drugs for the treatment of hypertension. Cilnidipine is a novel CCB with a dual L/N-type CCB property, thus favoring additional renal and cardiovascular protection. **Aims and Objectives:** The aims of this study were to evaluate the effects and their linearity across the time frame of amlodipine and cilnidipine in hypertensive subjects with proteinuria on heart rate and proteinuria. **Materials and Methods:** A prospective, randomized, open-label study was carried out on hypertensive subjects with proteinuria attending the General Medicine OPD in K.R Hospital, Mysore. 60 subjects satisfying the inclusion and exclusion criteria were included in the study. Heart rate and urine protein-to-creatinine ratio (UPCR) were measured at baseline and at 12 weeks along with weekly heart rate monitoring. The dose of amlodipine and cilnidipine was titrated depending on the blood pressure control. Descriptive statistics, independent sample *t*-test, repeated measure ANOVA, and Cramer's V-test were used to analyze the results. **Results:** Demographic profile was well matched in both the groups. The heart rate was significantly higher at 12 weeks in subjects treated with amlodipine, while subjects in the cilnidipine group showed a significantly higher heart rate compared to baseline ($P < 0.05$). Furthermore, while the UPCR was significantly decreased in the cilnidipine group, a significant increase was seen in the amlodipine group, thereby resulting in a significant intergroup difference ($P < 0.05$). **Conclusion:** Cilnidipine is, thus, a better alternative in hypertensive patients with proteinuria due to its cardioprotective and renoprotective actions.

KEY WORDS: Proteinuria; Heart Rate; Amlodipine; Cilnidipine

INTRODUCTION

Hypertension (HTN) is a major public health challenge as evidenced by its contribution to premature death not only in developing countries but also in developed countries as well.[1] The complications of long-standing HTN include coronary heart disease, congestive heart failure (CHF), stroke, renal impairment, and peripheral arterial disease.[2,3] Hence, timely detection and management forms the mainstay of managing hypertensive patients to prevent the cerebrovascular and cardiovascular complications.[4] The mortality due to these cerebrovascular and cardiovascular complications has seen a significant decline in the recent years owing to advances in the diagnosis and treatment of HTN and its complications.[5]

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Hypertensive nephropathy manifests as proteinuria which, in turn, results in increased risk of cardiovascular complications and further impairment of renal function.[3] Chronic and uncontrolled HTN not only favors the development of chronic kidney disease (CKD) but also hastens it progression, thus highlighting the importance of optimal blood pressure (BP) control in preserving renal function and thereby reducing morbidity and mortality from cardiovascular complications.[6]

Calcium channel blockers (CCBs) are a major class of drugs used in the treatment of HTN, forming the first-line agents irrespective of the stage of HTN, patient demographics such as age, gender, race, and presence of other comorbid conditions. The only exception to this is patients with coexisting renal disease, in whom renin–angiotensin system (RAS) blocking agents have been found to have better overall benefit.[7,8] Unlike angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), however, the ability to additionally reduce BP significantly with increasing dose is an added advantage with CCBs.[9]

Amlodipine is a L-type CCB with proven efficacy and safety in patients with HTN by providing optimal BP control over a 24 h period.[4] However, an important drawback with the use of amlodipine is the reflex increase in heart rate caused by the hypotensive effect.[5] It is also uncertain whether amlodipine has any significant renoprotective action.[10]

Cilnidipine is another dihydropyridine CCB which not only blocks L-type calcium channels but also the N-type calcium channels.[11] The additional N-type CCB property might not only help to suppress the reflex increase in heart rate but also provide added renal protection as shown by few studies.[7,12]

Hence, the present study was undertaken to evaluate the effects and their linearity across the time frame of amlodipine and cilnidipine in hypertensive subjects with proteinuria on heart rate and proteinuria.

MATERIALS AND METHODS

Study Site

Hypertensive subjects with proteinuria attending the General Medicine Department of K.R Hospital, Mysore, during January 2015 to December 2015.

Study Design

This was a randomized, parallel group, open-label, and single-center study.

Study Period

The study duration was January 2015–June 2016.

Sample Design

The sample design was a purposive sampling technique.

Sample Size

Using estimation technique with the prevalence of hypertensive subjects with proteinuria as 4%–16%, effect size 10% and level of significance as 5%, the sample size was calculated to be 15 and 53 for 4% and 16% prevalence, respectively. We decided to go with 60 subjects divided into two groups of 30 each.

Inclusion Criteria

The following criteria are included in the study:
- Age ≥ 40 years.
- Both sexes.
- HTN (Grades I and II) with coexisting proteinuria.
- Subjects who give informed consent.

Exclusion Criteria

The following criteria are excluded from the study:
- Subjects with systolic BP (SBP) ≥ 180 mmHg and/or diastolic BP (DBP) ≥ 110 mmHg before or during the washout period.
- Normotensive subjects with proteinuria.
- Hypertensive subjects on two or more antihypertensive medications.
- End-stage renal disease.
- CHF.
- Heart block.
- Aortic stenosis.
- Pregnant and lactating women.
- Subjects on amlodipine/cilnidipine/ACE inhibitors/ ARBs within 30 days before their enrolment into the study.

Method of Collection of Data

After getting clearance from the Institutional Ethical Committee, hypertensive subjects attending medicine OPD in K.R. hospital were screened for selection for the study. The subjects were well acquainted with the type of study and a written informed consent was taken.

A complete medical history was taken and physical examination was conducted. Later, following tests were performed:
1. ECG.
2. BP - subjects having uncontrolled HTN (SBP≥).
3. 140 mmHg and/or DBP ≥ 90 mmHg at the screening visit were excluded from the study due to ethical considerations.
4. Urine routine - only those subjects having urinary albumin 1+ or more on dipstick analysis were considered for the study.

5. Fasting blood sugar and post-prandial blood sugar.
6. Serum creatinine and blood urea nitrogen.
7. Echocardiography - If history and/or physical examination suggestive of CHF or aortic stenosis.

A 3 day washout period was given to all subjects whose screening visit was found satisfactory for inclusion into the study with daily BP monitoring during the washout period.

The subjects meeting the inclusion and exclusion criteria were then randomized into two groups of 30 each. A simple randomization procedure using a computer-generated random number table was adopted to randomize the subjects into two groups.

Group I: Received Tablet amlodipine 5–10 mg/day for 3 months.

Group II: Received Tablet cilnidipine 5–20 mg/day for 3 months.

Following parameters were recorded at baseline:

1. Heart rate: Measurement of heart rate: Using a finger probe pulse oximeter (easy care fingertip pulse oximeter).
2. Quantitative estimation of proteinuria – urine protein-creatinine ratio (UPCR): The protein content in urine was measured by turbidometric method in a spot urine sample using sulfosalicylic acid and sodium sulfate, and the urinary creatinine concentration was measured by Jaffe's reaction.[13] Urinary protein excretion in terms of mg/mg of urinary creatinine was calculated to give the UPCR.[14]

The dose of amlodipine and cilnidipine was titrated depending on the BP control. If the goal SBP and/or DBP as per JNC-8 guidelines for management of HTN was not reached at the end of 1 month of active treatment period, then those subjects were regarded as non-responders. The non-responders in Group I and Group II received increased dose of amlodipine or cilnidipine, respectively, for effective BP control. Otherwise, the same dose was continued throughout the study period.

Subjects were also informed about the known adverse effects of the respective drugs and were asked to report back anytime if necessary.

While BP and heart rate were recorded at weekly intervals thereafter, quantitative estimation of proteinuria was done at the end of 12 weeks of the evaluation period.

Statistical Analysis

Descriptive statistics and Cramer's V-test were used to analyze the demographic variables. Repeated measure ANOVA was used to analyze the variation in each parameter from baseline till the end of 12 weeks. For intergroup comparison, independent sample *t*-test was used. The entire data were analyzed using Microsoft Excel sheet and R software. $P < 0.05$ was considered to be statistically significant.

RESULTS

All 60 patients randomized and allocated to the treatment completed the study as per the protocol as shown in Figure 1. The demographic variables showed no significant difference between the two groups and are summarized in Table 1.

The mean dose of amlodipine in Group I was 5.2 ± 0.82 mg/day and the mean dose of cilnidipine in Group II was 10 mg/day at the end of the study. A number of subjects with type 2 diabetes mellitus in Group I and Group II were 16 and 12, respectively. Among these, 10 in each group were on metformin, while remaining diabetic subjects in amlodipine group (6) and cilnidipine group (2) were on a combination of metformin and glimepiride.

Effect on Heart Rate

The subjects in cilnidipine group had a significantly higher mean heart rate at baseline compared to the subjects in amlodipine group ($P < 0.049$). The change in mean heart rate from baseline was significant at 3 weeks, 6 weeks, and 12 weeks in both amlodipine group as well as cilnidipine group (ANOVA - $P < 0.001$) as shown in Figure 2. However,

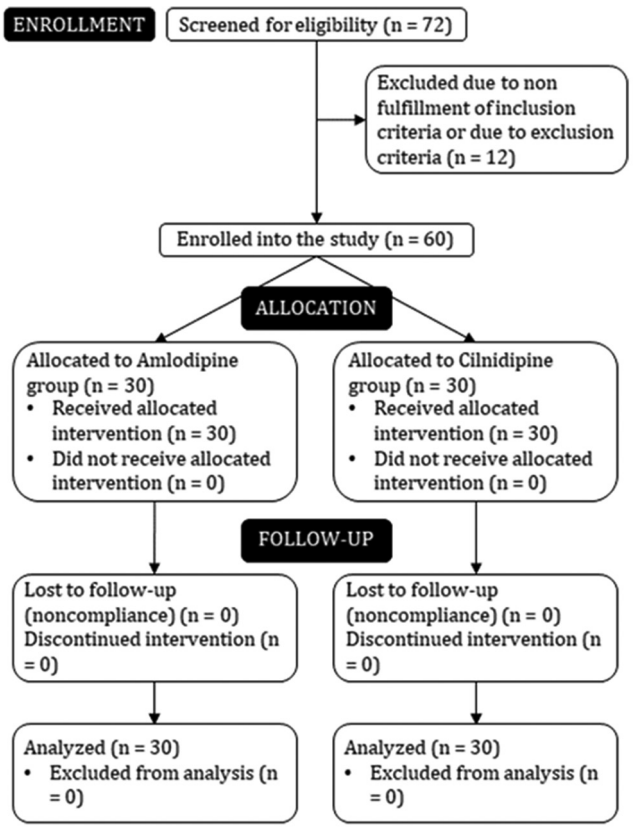

Figure 1: Study flow chart

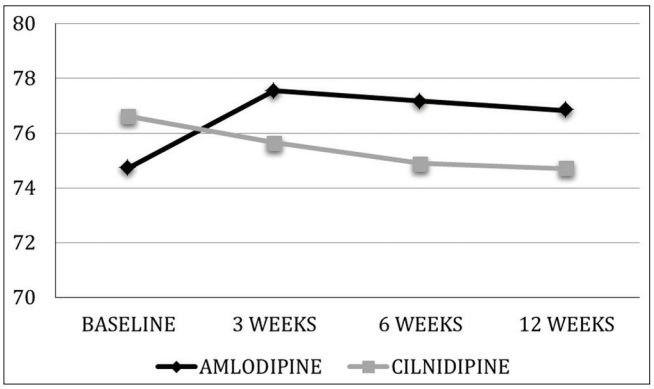

Figure 2: Mean heart rate in amlodipine group and cilnidipine group at specific intervals

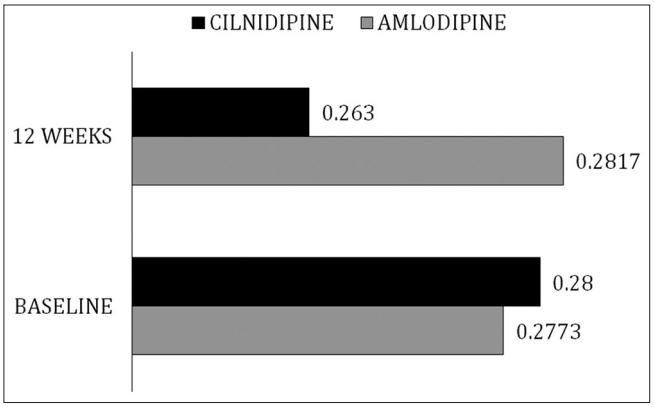

Figure 3: Mean urine protein-creatinine ratio in amlodipine and cilinidipine groups at baseline and at 3 months

the intergroup difference in the change in mean heart rate from baseline was significant only at 6 weeks and 12 weeks (independent sample *t*-test - $P < 0.01$) but not at 3 weeks (independent sample *t*-test - $P > 0.05$) of treatment with the study medications.

Effect on Proteinuria

The increase in mean UPCR in the amlodipine group and the decrease in mean UPCR in the cilnidipine group are both statistically significant (independent sample t-test - $P < 0.001$) as shown in Figure 3. Furthermore, the intergroup difference in the change in mean UPCR from baseline was statistically significant at 12 weeks of treatment (independent sample *t*-test - $P < 0.001$).

DISCUSSION

The efficacy of CCBs in maintaining optimal BP levels and thereby preventing cardiovascular and renal complications of HTN makes them an excellent class of antihypertensive drugs.[8] The present study aimed at evaluating and comparing the cardiovascular and renoprotective actions of two dihydropyridine - CCBs, and amlodipine and cilnidipine. The mean heart rate in subjects in amlodipine group increased significantly from 74.73 ± 3.64 bpm at baseline to 77.17 ± 4 bpm at the end of 3 weeks, 6 weeks, and 12 weeks.

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

On the contrary, the mean heart rate of subjects treated with cilnidipine 10 mg/day showed a statistically significant decrease from baseline (76.63 ± 3.68 bpm) toward the end of 3 weeks, 6 weeks, and 12 weeks (74.7 ± 3.55 bpm). In the amlodipine group, the UPCR increased from 0.2773 ± 0.03 mg/mg at baseline to 0.2817 ± 0.04 mg/mg at the end of 12 weeks which were statistically significant. In contrast to amlodipine group, subjects in cilnidipine group had a significant decrease in UPCR from 0.28 ± 0.03 mg/mg at baseline to 0.24 ± 0.03 mg/mg at 12 weeks of treatment. Furthermore, the intergroup difference in the change in mean heart rate from baseline was statistically significant at the end of 6 and 12 weeks of treatment, and similarly, there was a statistically significant difference in the change in mean UPCR values from baseline to 12 weeks between the amlodipine and cilnidipine groups.

In a study done by Kaur *et al.*,[9] the pulse rate was found to be significantly higher at the end of 6 weeks in 30 subjects who received amlodipine at a dose of 5–10 mg/day. An increase in daytime pulse rate has also been observed by Hoshide *et al.*[15] among 55 hypertensive subjects receiving amlodipine ≥2.5 mg/day. A similar statistically significant decrease in heart rate has been observed with cilnidipine, therapy in a study done by Manthri *et al.*[6] A study by Tanaka[16] has shown a significant decrease in heart rate with cilnidipine, therapy in 25 hypertensive subjects also having type 2 diabetes mellitus. Furthermore, a significant

decrease in heart rate with cilnidipine therapy has been observed in hypertensive patients with CKD on treatment with a RAS inhibitor in a study done by Hatta *et al.*[17] Our study also showed a significant difference in the change in mean heart rate from baseline at 6 weeks and 12 weeks between the amlodipine and cilnidipine groups. These results correlate well with the observations made in studies done by Zaman and Kumari,[18] Kaur *et al.,*[9] and Hoshide *et al.*[15] Ischemic events, stroke, heart failure, and renal failure are the consequences of ignoring sympathetic overactivity in patients with high BP according to 30.91%, 25.39%, 20.97%, and 22.30% physicians, respectively, according to a study done by Dalvi *et al.*[19] adding to the morbidity and mortality of such patients. The basis for a significant decrease in heart rate with cilnidipine therapy might be its dual L/N – type CCB property. Its inhibitory action on N-type calcium channels decreases norepinephrine release from the nerve terminals thus explaining its sympatholytic property.[11] Another study by Sakata *et al.*[12] has shown that cilnidipine suppresses cardiac sympathetic overactivity, while amlodipine had little such suppressive effect.

A statistically significant increase in proteinuria is in concordance with the observations made by Kojima *et al*.[20] and Fujita *et al*.[21] However, a study by Jalal *et al*.[22] has shown no significant change in urinary albumin excretion rate and another study by Janssen *et al*.[23] has shown no significant change in urinary protein excretion with amlodipine therapy. Factors such as daily protein intake and the presence of coexisting diabetes mellitus in our study subjects might explain such a difference observed. A significant decrease in proteinuria with cilnidipine therapy has been observed in a study done by Hatta *et al*.[17] Furthermore, studies by Makawana and Panchal.[24] and Manthri *et al*.[6] have all shown a significant decrease in urinary albumin excretion in hypertensive subjects treated with cilnidipine. Another study by Tsuchihashi *et al*.[25] has shown that cilnidipine reduces proteinuria in essential HTN but not in renal hypertensive patients. Our study also showed a statistically significant difference in the change in mean UPCR values from baseline to 12 weeks between the amlodipine and cilnidipine groups which are in concordance with studies done by Zaman and Kumari.,[18] Abe *et al*.,[26] Uchida *et al*.,[27] Fujita *et al*.,[21] and Kojima *et al*.[20] A significant decrease in albumin-creatinine ratio among hypertensive patients with type 2 diabetes mellitus was observed in a study done by Tanaka[16] which showed a positive correlation with the change in heart rate which shows inhibition of sympathetic activity by cilnidipine might be the basis of its renoprotective action. Cilnidipine, by virtue of blocking N-type calcium channels presents in the efferent arterioles and podocytes decreases the glomerular pressure thereby offering significant podocyte protection which contributes to its antiproteinuric effect.[28]

The strength of our study includes no bias in the allocation of subjects into amlodipine and cilnidipine groups since the whole process was randomized. Frequent monitoring of BP and heart rate at weekly intervals by the same investigator using the same equipment adds to the strength of our study. There was 100% compliance to treatment in both the groups and none of the subjects were lost to follow-up nor were withdrawn due to any concerns. The absence of any conflicts of interest is another plus point in our study.

Our study, however, had a few limitations. First, it was an open-label study with a small sample size. Second, since HTN is a chronic condition, an evaluation period of 3 months in our study was very short and required assessment of the study parameters over a longer duration.

CONCLUSION

The use of amlodipine is associated with reflex tachycardia and a significant increase in the urinary protein excretion rate which adversely affects the prognosis in hypertensive patients as opposed to cilnidipine which significantly decreases heart rate and proteinuria. Hence, we conclude that cilnidipine is a better alternative to amlodipine in hypertensive patients with proteinuria due to its cardioprotective and renoprotective actions.

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