Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study

Abstract
To compare amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in hypertensive individuals. This was a three months prospective, observational study done at the tertiary care center of Karnataka, India. A total number of 60 (n = 60) newly diagnosed hypertensives (≥140/90) of either gender, attending outpatient department of medicine, were included in the study. Out of 60 patients, 30 patients who have been prescribed tablet amlodipine 5–10 mg/day and the other 30 who have been prescribed tablet cilnidipine 10–20 mg/day orally by the consulting physician, depending upon the severity of hypertension were followed every fortnight, screened for the presence of pedal edema and blood pressure control over a period of 3 months. Antihypertensive efficacy between two groups was compared by unpaired t-test and incidence of pedal edema was compared by Fisher’s exact test. Of 30 patients in the amlodipine group, 19 patients presented with pedal edema (63.3%) and 2 patients (6.66%) in cilnidipine group presented with pedal edema during the study period. There was a significant difference in the incidence of pedal edema between amlodipine and cilnidipine group (P < 0.05), but no significant difference was found in the antihypertensive efficacy of amlodipine and cilnidipine (P > 0.05). Both amlodipine and cilnidipine have shown equal efficacy in reducing blood pressure in hypertensive individuals. But cilnidipine being N-type and L-type calcium channel blocker, associated with lower incidence of pedal edema compared to only L-type channel blocked by amlodipine.

Key words: Blood pressure, calcium channel blockers, N-type and T-type calcium channels

INTRODUCTION
Hypertension is the most common cardiovascular disease. Around 50 million individuals in the United States and 1 billion individuals worldwide are affected by hypertension.[1] The prevalence varies in different populations and ethnic group.[2, 3] In India, 29.8% population are suffering from hypertension.[4] Although there is dramatic age-related increase in the prevalence of hypertension, several important cardiovascular risk factors, particularly obesity, nutrient intake, physical activity, and diabetes also relate to the likelihood of hypertension. The Framingham heart study has estimated that individuals normotensive at the age of 55 years have a 90% lifetime risk of developing hypertension.[5] Hypertension represents a potent risk factor for cardiovascular, peripheral vascular, and renal diseases.[6–10]

The definition of hypertension as released by the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) is systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mm Hg, which simplifies hypertension classification by including only
Almost 9.3% of patients discontinue amlodipine therapy due to the adverse effects most commonly pedal edema. The most serious consequence of amlodipine induced edema is discontinuation of the effective antihypertensive therapy. Edema may result in the need for dose reduction or drug withdrawal, either of which can adversely affect the efficacy. A new generation of CCB, cilnidipine is an N-type and L-type CCB that also inhibits sympathomimetic activity in contrast to other DHP. Although L-type and N-type DHP CCBs are being used clinically, their specific effects on the pedal edema have not yet been elucidated. Hence, this study was taken to compare the antihypertensive efficacy and incidence of pedal edema with amlodipine and cilnidipine in hypertensive individuals.

**SUBJECTS AND METHODS**

A 3 months prospective, observational study conducted at the Tertiary Care Centre of Karnataka, India between November 2010 and June 2011. The study protocol was confirmed to the ethical guidelines of Declaration of Helsinki (Sixth revision, 2008). Approval of the Institutional Ethics Committee and patient consent were obtained prior to the study.

**Inclusion criteria**

Newly diagnosed as hypertensives (BP ≥ 140/90) of either gender in the age group of 35–75 years, attending outpatient department of medicine.

**Exclusion criteria**

Patients with preexisting edema, cor pulmonale, nephrotic syndrome, hypoproteinemia, anemia, pregnant women and who are on drugs such as nonsteroidal anti-inflammatory drugs and amantadine.

**Study procedure**

A total 60 patients (n = 60) who met the inclusion criteria were recruited in the study. The patients were examined by the consultant physician and blood pressure was measured in right arm, sitting posture by the auscultatory method using standard mercury sphygmomanometer. Two recordings of blood pressure were taken at an interval of 15–20 min by the same consultant. Pedal edema was assessed by clinical method over the medial malleolus of both legs. Presence of pedal edema on either of the legs is considered as positive for the pedal edema.

After initial screening, demographic data, past medical history, family history, and findings of clinical examination were recorded in the case report form. Of 60 patients, 30 patients who have been prescribed tablet amlodipine 5–10 mg/day and other 30 who have been prescribed tablet cilnidipine 10–20 mg/day orally by the consulting physician depending upon severity of hypertension, were included in this study. Patients were instructed to take the prescribed anti-hypertensive medication as per physician’s advice. Patient compliance was assessed by pill count method on every visit. All the 60 patients were followed every fortnight, screened for pedal edema and blood pressure control over a period of 3 months. Patients were instructed to consult the physician immediately in case of any unusual side effects (including pedal edema) if it occurs before the follow-up date.

**RESULTS**

All the 60 patients completed the study. Patient’s age for both the groups ranged between 30 and 75 years, with the...
mean age being 59.8 ± 9.7 years in the amlodipine group and 50.0 ± 9.8 years in cilnidipine group [Table 1]. Women (n = 17) were more than men (n = 13) in both the study groups. Both the groups were comparable in all aspects.

There was a significant reduction in systolic and DBP (P < 0.05) in both groups compared to baseline data [Table 2]. However, there was no significant difference in the antihypertensive efficacy of both drugs (P > 0.05).

Of 30 patients in cilnidipine group 2 patients (6.66%) presented with edema within 2 weeks of therapy, whereas 19 patients (63.3%) presented with edema (within 2 weeks of therapy) in amlodipine group [Table 3 and Figure 1]. Cilnidipine has shown significant reduction in the incidence of pedal edema when compared to amlodipine (P < 0.05).

There were no other significant adverse reactions observed in either amlodipine or cilnidipine group (other than pedal edema).

**Statistical analysis**

Antihypertensive efficacy between two groups was compared by unpaired t-test. The differences in the incidence of pedal edema between cilnidipine and amlodipine groups were compared by Fisher’s exact test. A P < 0.05 was considered statistically significant.

**DISCUSSION**

Clinical effects of DHP CCBs such as blood pressure lowering effect are mainly related to its action on L-type calcium channels. In contrast to arterioles, venules seem not to respond to L-type CCB or agonist. This was proved by many studies which have shown that nifedipine could not dilate venules of striated muscle in spontaneously hypertensive rats, and L-type calcium channel agonist could not constrict venules of frog skin.[17] Despite similar blood pressure reduction, the frequency of pedal edema varies between CCBs. Hence, its occurrence cannot be explained by a difference in their influence on peripheral arteries.[18] Therefore, drugs that specifically inhibit L-type channels like nifedipine, reduce the blood pressure by dilating resistance arterioles, but not venules, so that the pressure in the afferent capillaries peripheral to the resistance arteries increases above the oncotic pressure and extravasation occurs. In fact, a decrease in the frequency of pedal edema due to L-type calcium blockers is reported when these drugs are combined with ACEI, which have a vasodilatory effect on the venules.[19]

N-type calcium channels are distributed in the neurons and have an important role in regulating sympathetic activity.[20] Sympathetic nerves are found in the venules, so drugs that block N-type calcium channels possibly cause venodilation.[21]

Cilnidipine is a 1,4-DHP CCB that suppresses the influx of calcium ions via L-type and N-type calcium channels, thus reducing the blood pressure through vascular smooth muscle relaxation and arterial dilatation.[22-24] It is used as an antihypertensive agent with a long duration of action that allows once-daily dosing.[25] Cilnidipine is known to suppress catecholamine release from peripheral sympathetic nerves as it blocks N-type channels in sympathetic nerve

![Figure 1: Bar diagram showing incidence of pedal edema in both the groups](image)

**Table 1: Demographic data of the patients**

| Patients | Amlodipine | Cilnidipine | Total |
|----------|------------|-------------|-------|
| Number of patients | 30 | 30 | 60 |
| Age (years) | | | |
| Mean±SD | 59.8±9.7 | 50.0±9.8 | 54.9±9.7 |
| Range | 40-75 | 35-72 | 35-75 |
| Gender | | | |
| Male | 13 | 13 | 26 |
| Female | 17 | 17 | 34 |

SD: Standard deviation

**Table 2: Comparison of antihypertensive efficacy of amlodipine with cilnidipine**

| BP | Treatment | PreRx BP | PostRx BP | Difference | t* | P** |
|----|-----------|----------|-----------|------------|----|-----|
| SBP | Amlodipine | 162.0±7.8 | 138.9±10.9 | 23.1±8.8 | 14.35 | <0.001 |
|     | Cilnidipine | 164.7±9.5 | 143.6±6.8 | 21.1±9.2 | 12.58 | <0.001 |
|     | Amlodipine** versus cilnidipine | t=1.19 P=0.24, NS | t=2.01 P=0.04, S | t=0.89 P=0.38, NS | - | - |
| DBP | Amlodipine | 91.9±8.8 | 79.5±7.0 | 12.5±9.6 | 7.07 | <0.001 |
|     | Cilnidipine | 93.7±6.6 | 83.3±6.0 | 10.3 | 8.60 | <0.001 |
|     | Amlodipine** versus cilnidipine | t=0.81 P=0.42, NS | t=2.30 P=0.02, S | t=1.00 P=0.32, NS | - | - |

*Paired t-test, S: Significant, NS: Not significant, **Unpaired t-test. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BP: Blood pressure
Table 3: Details of patients presenting with pedal edema in both groups

| Data analyzed | Edema (%) | Without edema (%) | Total |
|---------------|-----------|-------------------|-------|
| Amlodipine    | 19 (63.3)** | 11 (36.7) | 30 |
| Cilnidipine   | 02 (6.66)** | 28 (93.3) | 30 |
| Total         | 21 (35)    | 39 (65)          | 60 |

*Fish’s exact test, **P<0.001

terminals as well as having a common L-type calcium channel-blocking effect.[26] It has been shown that cilnidipine does not cause coronary sympathetic hypertonia in response to blood pressure reduction, unlike L-type channel blockers.[27] When administered to the patients with essential hypertension, cilnidipine suppressed cardiac sympathetic over activity and an increase of heart rate with blood pressure reduction.[28] Previous study has also shown that cilnidipine is well-tolerated by the hypertensive patients and associated with minor adverse effects such as headache, dizziness, cough, and gastrointestinal symptoms which are comparable to amlodipine.[29]

Accordingly, CCBs with an N-type channel blocking effect may dilate the venules through sympathetic nerves distributed to these vessels. Hence have a lesser incidence of pedal edema compared with the other CCBs which act only on L-type calcium channels.

CONCLUSION

Both amlodipine and cilnidipine have equal efficacy in reducing blood pressure in hypertensive individuals. But cilnidipine being N-type and L-type CCB, associated with lower incidence of pedal edema compared to only L-type channel blocked by amlodipine.

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