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### Original Article

#### A Prospective clinical study to determine whether clinidipine a dual L/N-type CCB drug therapy can produce resolution of amlodipine induced edema while maintaining adequate control of blood pressure

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#### ABSTRACT:

**Background:** Pedal edema is a common adverse effect of amlodipine, an L-type calcium channel blocker, used as monotherapy for hypertension due to increased hydrostatic pressure across capillaries of dependent parts. Clinidipine is a newer dual L/N-type CCB approved for treatment of essential hypertension that produces balanced vasodilation of – 'pre and post capillary bed' blood vessels and thus no change in hydrostatic pressure, rather it mitigates it, hence lesser incidence of edema of dependent parts. **Materials and methods:** A total 100 patients of primary hypertension on amlodipine treatment who met inclusion criteria were recruited in the study. Those having pedal edema as a side effect were identified clinically. In them amlodipine was stopped and were treated with equivalent dose of Clinidipine. Baseline pedal edema was assessed by clinical method over medial malleolus of both legs before initiation of trial medication. Presence of pedal edema on either of the legs was considered as positive for the pedal edema. After initial screening – demographic data, past medical history, family history, and findings of clinical examination was recorded in the case report form. 27 patients out of 100, who were having pedal edema were instructed to take the prescribed anti-hypertensive medication; Clinidipine for 8 weeks duration as per physician's advice. All the alterations occurring in the ankle circumferences and the hemodynamic parameters were summarized and analyzed by SPSS software. **Results:** There was a significant reduction in ankle circumference of both the feet at the end of the study. However no significant reduction in the mean pulse rate and mean arterial blood pressure was seen at the end of the study in comparison to the baseline values. **Conclusion:** Treatment with clinidipine resolves amlodipine induced edema in all the patients without significant alterations in hypertension or tachycardia.

**Key words:** Amlodipine, CCB, Clinidipine, Pedal edema.

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#### INTRODUCTION:

Calcium channel blockers (CCBs) are an effective class of antihypertensive drugs but their use is associated with increased risk of peripheral edema especially when used as monotherapy, a side effect that may reduce patient compliance or necessitate switching over to a different drug.<sup>1-3</sup>

However, the incidence of edema in CCB-treated patients can be reduced by addition of an inhibitor of rennin-angiotensin system (RAS), that is an ARB or an angiotensin converting enzyme inhibitor (ACEI). CCBs induced edema is caused by increased capillary hydrostatic pressure that results from vasodilation of only pre capillary vessels. Advancing age increases the likelihood of CCB induced edema as the interstitial tissue ages.<sup>4-6</sup> Therefore it

is less able to counterbalance hydrostatically driven edema and thus the elderly patients are more likely to have greater levels of CCBs induced edema. Furthermore, an upright posture also increases the hydrostatic pressure of the legs and can result in an increased risk of incidence of CCB-induced edema. L-type calcium channel blockers are widely used for the treatment of hypertension.<sup>7-9</sup> Amlodipine acts primarily through blockade of L-type calcium channel whereas Clinidipine a 4<sup>th</sup> generation; CCB acts through dual blockade of L-type and N-type calcium channels. L-type calcium channel blockade produces vasodilation of peripheral resistance vessels and inhibition of neuronal N-type calcium channel disrupts sympathetic nervous outflow, lowering the plasma catecholamine levels and thereby producing further vasodilatation. This unique mechanism of action of clinidipine results in vasodilation of both pre and post capillary resistance vessels reducing capillary hydrostatic pressure and consequent hyperfiltration of fluid into the interstitium. This explains both the low incidence of pedal edema and the excellent antihypertensive action of clinidipine. Adake P et al; compared amlodipine with clinidipine on antihypertensive efficacy and incidence of pedal edema in hypertensive individuals. This was a three months prospective, observational study done at tertiary care center of Karnataka, India. A total number of 60 (n=60) newly diagnosed hypertensives ( $\geq 140/90$ ) 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 clinidipine 10-20mg/day orally by consulting physician, depending upon the severity of hypertension were followed every fortnight and 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 clinidipine group presented with pedal edema during the study period. There was a significant difference in the incidence of pedal edema between amlodipine and clinidipine groups, but no significant difference was found in the antihypertensive efficacy of amlodipine and clinidipine. Hence; we planned the present study to prospectively analyze whether clinidipine a dual L/N type CCB drug therapy can produce resolution of amlodipine induced edema while maintaining adequate control of blood pressure.

#### **MATERIALS AND METHODS:**

IEC clearance was obtained prior to initiation of the study. Informed consent for participation was taken from all the patients enrolled in the study. One year prospective observational study was conducted in department of

medicine at the tertiary care center of MMMCH at Solan H.P., India. A total of 100 patients of primary hypertension who met the inclusion criteria were recruited in the study and they were already taking amlodipine as an antihypertensive treatment. They were screened for pedal edema as a side effect of amlodipine and those having pedal oedema were substituted with an equivalent dose of clinidipine (5 mg amlodipine = 10 mg clinidipine) for 8 weeks duration. The patients were examined by consultant physician and blood pressure was measured in right arm in sitting posture by the auscultatory method using standard mercury sphygmomanometer. Two recordings of blood pressure were recorded 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 was considered as positive for the pedal edema. Circumferences of both the ankles were also recorded in centimeters for the measurement of pedal edema. After initial screening, demographic data, past medical history, family history and findings of clinical examination was recorded in the case report form. All the 27 patients with pedal edema were instructed to take clinidipine medication as per physician's advice. Patients were advised to consult the physician immediately in case of any unusual side effects if it occurs before the follow up dates which were at after 4 weeks and then at 8 weeks of trial medication.

**Inclusion criteria:** Patients of primary hypertension who were already taking amlodipine as antihypertensive treatment.

**Exclusion criteria:** Patients with pre existing edema, cor pulmonale, nephrotic syndrome, hypoproteinemia, anaemia and those who were on nonsteroidal anti-inflammatory drugs, amantadine, pregnant and lactating women.

**Statistics:** All the alterations occurring in the ankle circumferences and the hemodynamic parameters was summarized and analyzed by SPSS software. Chi-square test was used for assessment of level of significance.

#### **RESULTS:**

52 percent of the patients were more than 40 years of age, while the remaining 48 percent were less than 40 years of age. Mean age of the patients of the present study was 41.6 years. 60 percent of the patients of the present study were males while the remaining 40 percent were females. Mean baseline value of right ankle circumference was 27.5 cm, while the value at the end of the study was 24.1 cm. Mean baseline left ankle circumference was 25.6 cm, while value at the end of study was 22.7 cm. There was a significant reduction in the ankle circumference of both the feet at the end of the study. However, no significant reduction in the mean pulse rate and mean arterial blood pressure was seen at the end of the study in comparison to the baseline values.

**Table 1:** Demographic data

Parameter		Value
Age group (Years)	less than 40	48
	More than 40	52
Mean age (Years)		41.6
Gender	Males	60
	Females	40

**Table 2 :** Comparison of parameters at the baseline and at the end of the study

Parameter	Value at baseline	Value at the end of study	p Value
Mean right ankle circumference (cm)	27.5	24.1	0.02*
Mean left ankle circumference (cm)	25.6	22.7	0.02*
Mean body weight (kg)	68.9	66.2	0.04*
Mean pulse rate (bpm)	77.8	77.5	0.25
Mean arterial BP (mm of Hg)	105.4	106.8	0.77

\*: Significant

**DISCUSSION:**

In the present study, a total of 100 patients were analyzed. 52 percent patients were more than 40 years of age while 48 percent were less than 40 years. Mean age of the study patients was 41.6 years. Shetty R et al<sup>10</sup> determined whether cilnidipine can produce resolution of amlodipine- induced edema while maintaining adequate control of hypertension. In this prospective study 27 patients of essential hypertension were detected with amlodipine induced edema. Concomitant nephropathy, cardiac failure, hepatic cirrhosis or other causes of edema and secondary hypertension were excluded by appropriate tests. Amlodipine therapy was substituted in all these 27 patients with an efficacy-equivalent dose of cilnidipine. Clinical assessment of ankle edema and measurement of bilateral ankle circumference, body weight, blood pressure and pulse rate were performed at onset of the study and then after 4 weeks and 8 weeks of cilnidipine therapy. At completion of the study, it was found that edema had resolved in all the patients. There was a significant decrease in bilateral ankle circumference and the body weight. There was no significant change in mean arterial blood pressure and pulse rate. Therapy with cilnidipine resulted in complete resolution of amlodipine- induced edema in all the cases without significant worsening of hypertension or tachycardia.<sup>10</sup> Adake P et al; compared amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal oedema in hypertensive individuals and found that cilnidipine substitution resolves pedal edema due to amlodipine therapy while maintaining adequate control of blood pressure.<sup>11</sup> In our study 60 percent of the patients were males and 40 percent were females. Mean baseline value of right ankle circumference was 27.5 cm while mean value at the end of the study was 24.1 cm. Mean left ankle circumference at the baseline was 25.6 cm, while mean left ankle circumference at the end of the study was 22.7 cm. There was a significant reduction in the ankle circumference of both the feet at the end of the study.

However no significant reduction in the mean pulse rate and mean arterial blood pressure was seen at the end of the study in comparison to the baseline values.

**CONCLUSION:**

Cilnidipine a 4<sup>th</sup> generation CCB with dual mode of action on L and N type calcium channel resolves amlodipine - induced edema in all the patients while maintaining adequate control of blood pressure.

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