

Cilnidipine for Amlodipine Induced Pedal Edema and its Anti-hypertensive Effect in a Tertiary Care Teaching Hospital of Western Nepal

Ram Chandra Kafle,¹ Subash Sapkota,¹ Abhisek Maskey²

ABSTRACT

Background: Hypertension is the most common cardiovascular disease. In Nepal, 27.3% populations are suffering from hypertension. Amlodipine is the most frequently prescribed anti-hypertensive drug. Up to 15% of patients develop pedal edema with amlodipine that may lead to discontinuation. Cilnidipine, a new calcium channel blocker, found equally effective and edema is uncommon in different studies from India. We aimed to study anti-hypertensive effect and to assess resolution of amlodipine induced Pedal edema with cilnidipine.

Methods: This was a prospective, single centre observational study. Study was conducted in the department of cardiology, Manipal teaching hospital from 7th May to 6th November 2020. Hypertensive Patients who were on amlodipine for at least 6 months and presented with pedal edema were enrolled for the study.

Results: Total of 107 patients were enrolled for the study. The mean age of patients was 56.35 ± 12.84 years, ranged from 29 to 85 years and more than half (52.3 %) were male. Of the 107 patients, 90 (84.1%) patients received 10mg of cilnidipine. On follow up, all patients except three (2.8%) had resolution of pedal edema. The blood pressure reduction with cilnidipine was comparable with amlodipine ($p > 0.05$). Three patients who had persistent edema on follow up were on higher dose of cilnidipine.

Conclusions: The newer L and N type CCB, Cilnidipine has comparable efficacy with amlodipine and well tolerated in our population. Though the incidence of pedal edema is low but can occur with cilnidipine especially with higher doses.

Keywords: Amlodipine; ankle edema; cilnidipine; hypertension

INTRODUCTION

Hypertension is the most common cardiovascular disease. In Nepal, 27.3% populations are suffering from hypertension.¹ Hypertension represents a potent risk factor for cardiovascular, peripheral, vascular, and renal diseases.^{2,3} Pedal edema which is seen in up to 15% of patients in various studies, is one of the commonest adverse effect of Amlodipine, an L-type calcium channel blocker (CCB).^{4,7} Previous Meta-analysis of randomized controlled trials and prospective comparative trials showed that cilnidipine, new L and N type of CCB is equally effective and safe when compared with Amlodipine.^{8,9}

Cilnidipine is available for amlodipine induced edema in our region recently. Studies from India found that pedal edema is uncommon with cilnidipine^{9,10} substitution of amlodipine with cilnidipine could provide similar control of blood pressure and prevent discontinuation

of essential and effective drug. So, we aimed to study resolution of amlodipine induced edema with cilnidipine and its effectiveness in our population.

METHODS

This was prospective single centre observational study. Study was conducted at Manipal Teaching Hospital, a tertiary care Centre of Western Nepal from 7th May to November 6th 2020. All consecutive patients who were on amlodipine for at least 6 months and presented to cardiology OPD with complaint of pedal edema were enrolled. Patients with major organ failure, Endocrine abnormalities, Secondary hypertension, Varicose vein, venous insufficiency, Hypoalbuminemia or hypoproteinemia, Lymphedema, Pulmonary hypertension, Pregnant women, patients on HRT, Patients on any other class of antihypertensive agents, non-steroidal anti-inflammatory drugs & Steroids and other cause of edema with appropriate tests were excluded.

Correspondence: Ram Chandra Kafle, Department of Cardiology, Manipal college of Medical Sciences, Pokhara, Nepal. Email: drkafle30@gmail.com, Phone: +9779856034493.

The edema that cause discomfort to the patient and seeks doctor’s advice was considered as significant edema. Pedal edema was assessed and confirmed by clinical method over the medial malleolus or lower third part of shin of both legs. Echocardiographic measurements were obtained by cardiologists using a 2D color and Doppler echo system (Siemens ACUSON SC2000 PRIME, Berlin, Germany) according to the recommendations of the American Society of Echocardiography (ASE).¹¹ IVC diameter was measured at end-expiration and just proximal to the junction of hepatic vein.¹²

All enrolled patients were given equivalent dose of cilnidipine (5 mg of amlodipine is equivalent to 10 mg of cilnidipine) as a part of routine patients care. Amlodipine therapy was stopped on the day of initiation of cilnidipine. All patients were re-evaluated after one month of therapy, as previous studies showed complete resolution of edema over one month period.¹⁰

Data was analyzed using the software SPSS for windows version 18. Categorical data was compared using chi-square test and continuous data were compared using Students T test. The risk estimate was calculated using relative risk or Odds ratio as appropriate. Differences was considered significant at a predetermined α level of 5%.

Approval to conduct this research was obtained from the Institutional Review committee, Manipal College of Medical Sciences, Pokhara, Nepal. No data were obtained from study participants until they had provided informed written consent and the collected data were secured and made accessible only to investigator to maintain confidentiality.

RESULTS

Table 1. Socio-demographic characteristics of the respondents (n = 107).

Variables	Frequency (f)	Percentage (%)
Age (in years)		
< 45	15	14.0
45 - 75	80	74.8
>75	12	11.2
Mean \pm SD	56.35 \pm 12.84	
Gender		
Male	56	52.3
Female	51	47.7

Total of 107 cases were enrolled for the study. The mean age of patients was 56.35 \pm 12.84 years, ranged from 29 to 85 years and more than half (52.3%) were male.

showed that nearly 3/4th of the respondents were of age group 45 - 75 years (Table 1).

Table 2. Laboratory parameters of patients(on Amlodipine) with pedal edema (n=107).

Variables	Urea	Creatinine	TSH	Total protein	Albumin	LVEF
Mean \pm SD	26.95 \pm 6.54	0.93 \pm 0.23	3.35 \pm 0.98	7.18 \pm 0.42	3.99 \pm 0.41	63.31 \pm 2.81
Minimum	16	0.60	0.98	6.5	3.50	58
Maximum	36	1.30	5.50	8.1	5.0	69

The laboratory parameters in patients who were taking Amlodipine and presented with pedal edema are shown in table 2. All tests including renal, liver, thyroid and heart function were within normal limit and the cause edema is presumed to be drug (Amlodipine)

Table 3. Comparison of the parameters between Amlodipine and Clindipine (n = 107).

Variables	On Amlodipine Mean \pm SD	On 4 weeks Clindipine Mean \pm SD	P value
Body weight	65.21 \pm 4.58	63.75 \pm 4.07	<0.001
Body mass index (BMI)	24.46 \pm 1.32	23.92 \pm 1.11	<0.001
Systolic BP (mmHg)	132.07 \pm 6.80	132.62 \pm 6.94	0.158
Diastolic BP (mmHg)	84.02 \pm 4.16	85.38 \pm 4.12	0.884
Pulse rate	77.94 \pm 10.02	78.00 \pm 9.25	0.837

There was significant reduction of body weight and BMI after four weeks of clinidipine. As edema was subsided in majority of patients, BMI was significantly lower after 4 weeks of clinidipine therapy. There was reduction of BP (both systolic and diastolic) and pulse rate but not statistically significant (Table 3).

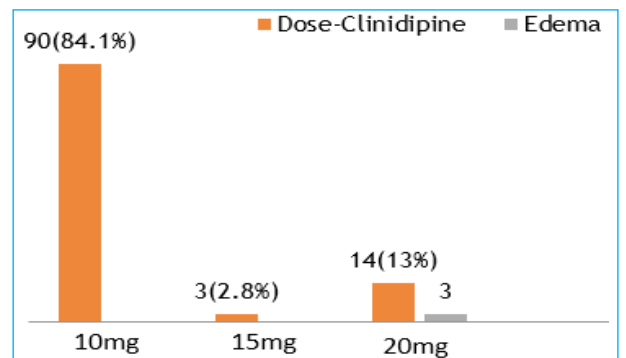


Figure 1. Dose of clinidipine and edema.

Figure 1 illustrate that majority (84.11%) of patients were taking lower doses (10mg) of clinidipine. Pedal edema

was persistent at four weeks in three (2.8%) patients who were taking higher (i.e. 20mg) dose of clinidipine. It appears that the pedal edema is dose dependent.

DISCUSSION

Hypertension is the most common cardiovascular disease. In Nepal, 27.3% populations are suffering from hypertension.¹ Calcium channel blocker (amlodipine) is one of the first line drug listed in all published guidelines. No lab reports required to start or titrate dose of CCB and can be prescribed by medical officer or even by trained paramedics in low resource setting and remote areas. So it is one of the most commonly prescribed drug worldwide. Pedal edema is a common side effect of amlodipine. The reported incidence of pedal edema with amlodipine is upto 15% in previous studies.^{4,5} The mechanism of pedal edema in patients taking L-type CCB is related to selective dilatation of afferent arterioles but not venules. Lower incidence of Pedal edema with combination therapy of calcium channel blocker and ACE inhibitors is thought to be due to their vasodilatory effect on the venules.¹³ L and N-type calcium channels blockers cause dilatation of venules as well through sympathetic nerves distributed around it.^{14,15} The mean age of patients was 56.35 ± 12.84 years, ranging from 29 to 85 years. In our study, edema was persistent at four weeks in three (2.8%, n=107) patients which was lower than study from Dehradun, India, by uniyal N. et al showed clinidipine induced edema in eight percentage (n=50) in treatment naïve patients.¹⁶ In contrast, study from south india by Kiran Shetty¹⁷, study from Kasturba Hospital, Manipal, southwestern india by Ranjan Shetty¹⁸ and central india by Ravi Shankar¹⁰ showed complete resolution of amlodipine induced edema with clinidipine. Thus the vasodilatory effect of both arterioles and venules by L and N type CCB is associated with a lesser incidence of pedal edema compared to only L-type blocking CCB. The clinidipine showed comparable anti-hypertensive effect compared to amlodipine in our study (P: 0.158 for SBP and 0.884 for DBP). In a systematic review and meta-analysis of randomized controlled trials in Chinese population with mild to moderate hypertension by Xu G et al⁸, similarly studies from India, by Adake P et al, (manglore)⁹ and from Telangana by K. Anantha Babu¹⁹ showed clinidipine was equally effective and safe compared to amlodipine. Amlodipine has dose-dependent edema²⁰, similarly in our study edema was persistent at four weeks of clinidipine therapy in patients who were taking 20mg but not with lower doses which appears dose-dependent. There are few limitations of our study. This is a single centre study with limited sample size. Due to non-probability

convenient sampling and single centre study, the result may not represent the population of all region of Nepal.

CONCLUSIONS

The newer L and N type CCB, Clinidipine showed comparable anti-hypertensive effect with amlodipine and well tolerated in our population. We observed lower incidence of pedal edema with clinidipine especially with lower doses but future prospective studies with larger sample size are needed to conclude.

Author Affiliations

¹Department of Cardiology, Manipal College of Medical Sciences, Pokhara, Nepal

²Department of Internal Medicine, Manipal College of Medical Sciences, Pokhara, Nepal

Competing interests: None

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