Research Article

Demonstration of Resolution of Amlodipine Induced Pedal Edema by Cilnidipine

Kiran Shetty[1], Ranjan Shetty[2*], Pragna Rao[3], Deepak[3], Sravan Reddy[5], Vidya Nayak[6]

1) Kiran Shetty, PhD Scholar, Dept. of Cardiology, KMC, Manipal University, Manipal.
2) Ranjan Shetty*, Professor, Dept. of Cardiology, KMC, Manipal University, Manipal.
3) Pragna Rao, Professor, Dept. of Biochemistry, KMC, Manipal University, Manipal.
4) Deepak, PhD Scholar, Dept. of Cardiology, KMC, Manipal University, Manipal.
5) Sravan Reddy, Senior registrar Dept. of Cardiology, KMC, Manipal University, Manipal.
6) Vidya Nayak, Asst.Professor Dept. of CVT, SOHAS, Manipal University, Manipal.

***Corresponding author's E-mail:** sampkiran@gmail.com & ranjanshettyk@yahoo.com

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ABSTRACT

The aim of the study is to demonstrate the resolution of Amlodipine induced pedal edema by substitution of Cilnidipine with an adequate hypertension control. This was a prospective, Interventional study. Conducted at the tertiary care center in south India. A total number of 66 (n = 66) patients with essential hypertension with the amlodipine-induced edema of both genders, attending the outpatient department of medicine and cardiology, were included in the study. Amlodipine induced pedal edema was confirmed by various tests. After the Initial screening, amlodipine therapy was substituted to Cilnidipine with an efficacy equivalent dose. Clinical and biochemical parameters measured at the onset of the study and reassessed after 4 weeks of Cilnidipine therapy. At the end of the study, amlodipine-induced pedal edema was completely resolved in all the patients. There was a significant decrease in vanillyl mandelic acid (VMA) and (P <0.001), which is end metabolite of catecholamine. There was a substantial reduction in bilateral ankle circumference, Body weight and BMI (P <0.001). There was a significant decrease in blood pressure and pulse rate (P <0.001). Cilnidipine therapy leads to a complete resolution of amlodipine-induced edema, along with a better hypertension control. Cilnidipine is decreasing the release of catecholamine by inhibiting N-type of calcium channels at the neuronal terminal. Cilnidipine is a suitable alternative antihypertensive medication for patients with the amlodipine-induced edema.

Keywords: Amlodipine, Cilnidipine, Vanillyl Mandelic Acid, Pedal Edema.

INTRODUCTION

The global burden of hypertension is extremely high and is a leading cause of premature deaths. Worldwide, one billion people are affected by hypertension, in India, 29.8% of people are suffering from high blood pressure.[1] The Framingham Heart Study explains that above 55 age, the lifetime risk of developing hypertension is about 90%, the prevalence of hypertension is high in low-income developing nations than the high income developed countries.[2] High blood pressure is a possible risk factor for cardiovascular, peripheral, cerebrovascular and renal diseases, including eye.[3-6]

In hypertensive patients, achieving blood pressure control requires changes in lifestyle or potential antihypertensive drug therapy or both. Anti-hypertensive medications include Diuretics, Calcium channel blockers, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, sympatholytic drugs, and vasodilators. These antihypertensive groups of the drug can be used in monotherapy or in combination therapy, the choice or drugs depends on patient's condition and other related risk factors.[7, 8]

According to studies, use of CCBs as an antihypertensive therapy with high-risk patients (elderly patients, Type 2 Diabetic Mellitus, Coronary artery diseases, co-morbid Raynaud syndrome, angina pectoris, Peripheral vascular diseases, cerebrovascular diseases and pregnancy) is more beneficial.[9]

Among Dihydropyridine group of calcium channel blockers, Amlodipine is a powerful, long-acting, third generation L type of Calcium channel blockers. Pedal edema is the major adverse effect of amlodipine therapy. The Incidence of pedal edema ranges from 1.7% to 63.3% in different clinical studies were monotherapy showed a higher incidence than combination therapy.[10,11] The typical way to deal with amlodipine-induced pedal edema patients includes the end of amlodipine therapy and substitution with an alternative class of antihypertensive drug.[12] Cilnidipine is novel, fourth generation L/N type of calcium channel blocker[13], and it is clinically being used for antihypertensive therapy, many recent studies concluded that Cilnidipine has a good tolerability and also have a good blood pressure control equivalent to amlodipine.[14] Cilnidipine showed a complete resolution of amlodipine-induced pedal edema[15], Cilnidipine is a dual L/N-type CCBs, The blockade of N-type calcium channels effectively suppresses the sympathetic nervous system.[16-18] This study was, therefore, planned to evaluate the causative factors in Amlodipine induced pedal edema and demonstration of resolution in edema with a substitution of Cilnidipine.

MATERIALS AND METHODS

This was a prospective, Interventional study. Total sixty-six hypertensives [≥140/90] amlodipine-induced pedal edema patients are included of both genders. All recruited patients have completed the study. This study was conducted between dates in January 2014 to May 2016 at a tertiary care center, Karnataka, India. The study protocol was confirmed, Approval of the Institutional Ethics Committee and patient consent were obtained prior to the study.

Inclusion criteria

Hypertensive, AIPE patients of both genders [>140/90 mm Hg], Patients currently receiving amlodipine more than six months for the Treatment of HTN, Age limit is 18 to 70 years, Amlodipine induced pedal edema [with no other obvious cause].

Exclusion criteria

Patients with major organ failure, Endocrine abnormalities, Pregnant women, patients on HRT, Patients on any other class of antihypertensive agents, nonsteroidal anti-inflammatory drugs & Steroids, Lymphedema, Pulmonary hypertension, Secondary hypertension, Varicose vein, Venous insufficiency.

Study procedure:

A total sixty-six patients [n = 66] who met the inclusion criteria were recruited in the study. The patients were examined by the consultant cardiologist and blood pressure was measured in the right arm, sitting posture by the auscultatory method using a standard mercury sphygmomanometer. The three readings are recorded at an interval of 10 min and mean of three blood pressure readings and pulse rate was noted. Pitting pedal edema was confirmed by the clinical method over the medial malleolus of both legs. After initial screening, demographic parameters, family history, clinical examination findings and biochemical parameters were noted. After baseline reading, amlodipine is changed to an equipotent dose of Cilnidipine and followed up for one month, repeated all the parameters.

Statistical analysis

Data analysis done by SPSS software (Vrsn. 20), were as continuous variables are compared by Paired t-test and were skewed distribution variables are compared with Wilcoxon test, p <0.05 was considered statistically significant.

RESULTS

This was a prospective Interventional study, we included 66 patients, all recruited patients were completed the study. Patient's age (mean ± SD) 57.65±10.12 and ranges from 38 to 70 years. 34 (51.5%) Men and 32 (48.5%) of women's are enrolled in this study, 34 (51.5%) patients are type- 2 Diabetic Mellitus, 20 (30.3%) patients are hyperlipidemia and 15 (22.7%) patients are smokers and 17 (24.8%) patients are having a family history coronary artery diseases. All 66 patients showed complete resolution of amlodipine-induced pedal edema at an average 6.7 days. Other demographic parameters are listed in Table No. 1.

Table 1: Baseline Demographic Parameters

VARIABLES		
Number of patients		66
Age[years]	Mean ± SD	57.65±10.12
	Range	31-70
Gender[M/F]	Male	34 (51.5)
	Female	32(48.5%)
Height [Cm]	Mean ± SD	157.07±10.02
	Range	131-176
Diabetic Mellitus	Present	34(51.5%)
	Absent	32(48.5%)
Hyperlipidemia	Present	20(30.3%)
	Absent	46(69.7%)
Smoking status	smoking	15(22.7%)
	Non smoking	51(77.3%)
Family history of CAD	Present	17(24.8%)
	Absent	49(74.2%)

We noted the baseline hemodynamic, clinical and biochemical parameters of amlodipine-induced pedal edema group, and after switching to Cilnidipine followed up for one month and reassessed all the baseline parameters. There was a significant reduction in body weight and BMI at the end of the study. Systolic and diastolic blood pressure and pulse rate showed a significant reduction after switching to Cilnidipine. Complete resolution of ankle edema seen at the end of the study, findings is reported in table No. 2.

Table 2: Comparison of Clinical parameters between Amlodipine induced pedal edema group [AIPE] and After Cilnidipine Treatment [ACT].

Variables	AIPE[n=66] [mean ± SD]	ACT [n=66] [mean ± SD]	P-value*
Body Weight [Kg]	61.80±9.03	59.53±9.54	< 0.001
Body Mass Index[BMI]	25.02±2.9	24.10±2.9	< 0.001
Systolic BP [mmHg]	142.42±3.6	139.97±3.8	< 0.001
Diastolic BP [mmHg]	84.32±4.8	80.16±4.3	< 0.001
Pulse Rate	77.42±9.9	75.63±8.44	< 0.05
Right Ankle Circumference	24.69±1.39	22.48±1.23	< 0.001
Left Ankle Circumference	24.65±1.43	22.54±1.25	< 0.001
LV ejection Fraction [%]	65.13±4.9	65.37±4.4	0.309
IVC [mm]	15.36±1.4	15.28±1.1	0.604
IVC[constriction]	6.78±1.01	6.56±1.11	0.129

* All continuous variables are compared by Paired t-test. P<0.05

VMA, serum osmolality showed a significant reduction at the end of the study, Plasma proteins, LV ejection fraction, Serum creatinine and serum Na++ remained same, did not show any significant difference, at the end of the study (P is >0.05) these all the findings detailed in table No.3.

Table 3: Comparison of Routine biochemical parameters between Amlodipine induced pedal edema group [AIPE] and after Cilnidipine Treatment [ACT],

Variables	AIPE[n=66] [mean ± SD]	ACT [n=66] [mean ± SD]	P-Value*
Serum creatinine [mg/dL]	0.97±0.23	1±0.17	0.081
Serum Na+ [mmol/L]	139.57±3.14	139.56±2.84	0.965
VMA [mg/24 hrs.]	6.87±2.35	5.12±1.5	<0.001
Serum osmolality [mosml/kg]	288.34±12.1	278.01±11.9	<0.001
Total protein [g/dL]	7.59±0.45	7.58±0.44	0.893
Serum albumin [g/dL]	4.48±0.55	4.35±0.29	0.077
Serum Globulin [g/dL]	3.06±0.37	3.08±0.44	0.594

* All variables are compared by Paired t-test. P<0.05

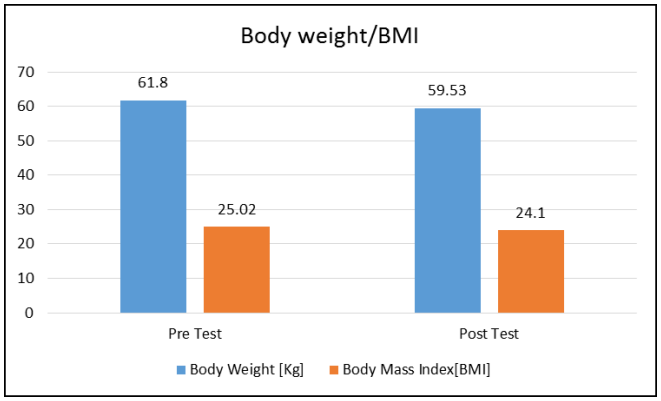

Figure 1: Bar-diagram showing Comparison of Body weight and BMI between Start [AIPE] and End of the study [ACT]. Were, at the end of the study [ACT] Body weight and BMI was significantly decreased (p<0.001).

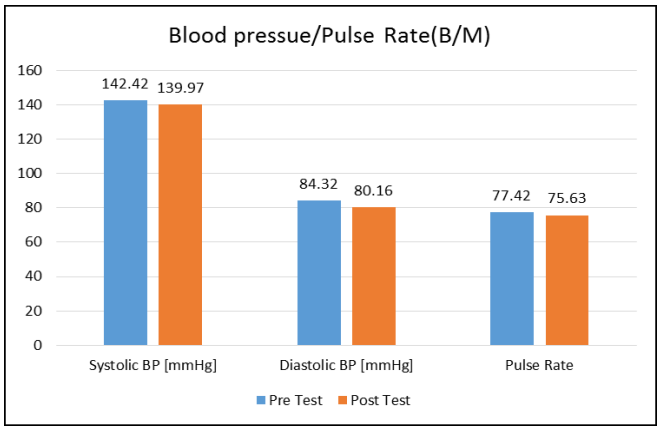

Figure 2: Bar-diagram showing Comparison of Systolic and Diastolic Blood Pressure, and Pulse Rate between Start [AIPE] and End [ACT] of the study. Were, at the end of the study [ACT] BP and PR was significantly decreased (p<0.001).

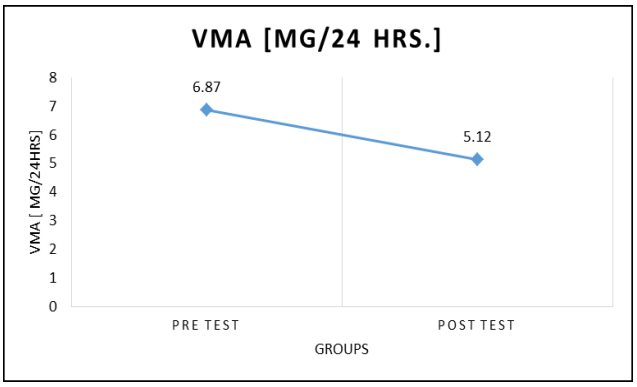

Figure 3: Line diagram showing Comparison of Vanillyl Mandelic Acid between Start [AIPE] and End [CTD]] of the study. Were, at the end of the study [CTD] VMA was significantly decreased (p<0.001).

DISCUSSION

According to JNC-8 calcium channel blockers are the foremost choice of antihypertensive drugs, the third generation DHP group of CCBs. Amlodipine has an excellent pharmacological profile. Amlodipine induced pedal edema is the major adverse event of amlodipine therapy. Adake, et al. (2015), conducted a prospective observational study, to assess the incidence of peripheral edema between amlodipine and cilnidipine groups. They concluded that amlodipine treatment group showed a higher incidence of pedal edema than cilnidipine group, along with good hypertension control. Morimoto S, et al. conducted a randomized trial to assess the efficacy of Cilnidipine on white coat effect, where cilnidipine attenuated the white coat effect. There are many other factors influences the pedal edema. Condition like, obesity, sleep apnea, and venous insufficiency may be predisposing factors for the cause of pedal edema. Women's are more conscious and comparatively higher rate of self-observation so women's are more likely to report peripheral edema.[19] As age advances, the vascular and interstitial muscle will also ages, so it's unable to counter the high hydrostatic pressure, which leads to peripheral edema and even upright posture also increases the lower limb hydrostatic pressure it may lead to ankle edema.[20] Various studies have been explained regarding the mechanism of CCBs Induced peripheral edema. The Important one is interference of normal auto-regulatory postural vasoconstrictor reflexes.[14] In normal, healthy individuals in response to venous congestion, the capillary bed is protected from increased hydrostatic pressure by activating arteriolar constriction reflex.[21]

There are many other mechanisms that contributing for induction of edema, i.e., increased hydrostatic pressure and microvascular permeability. The colloid osmotic pressure is influenced by proteins, so decreased plasma protein may lead to edema formation.[22] In the present

study, there were no significant changes between pre and post test.

Chronic therapy of amlodipine enhances to release of more catecholamines [23,24] ,the released catecholamines will act on adrenergic receptors, where amlodipine acts only on arterioles and dilates it, and it does not have action on veins.[7] Venules will be constricted by the action of catecholamines. Therefore, there will be an imbalance between pre and post-capillary flow, it may contribute to the establishment of peripheral edema.

Cilnidipine is a fourth generation calcium channel blocking agent, which acts on both L/N types of calcium channels.[25] Arteriolar dilation did by blocking an L - type of Ca channels. N-type Ca++ channels are present in the neurons and have a principal role in the regulation of sympathetic activity. Sympathetic nerve endings are spread over the venules, by blocking N-type calcium channels, interrupts sympathetic nervous system, decreases the release catecholamine from neuronal terminals, so Cilnidipine possibly causes venular dilation.[26, 27] Ogura C, et al. (2012) compared the effect of different types of CCBs, they concluded that monotherapy with Cilnidipine suppresses cardiac sympathetic nerve activity more effectively than amlodipine.[28] This unique mechanism of action of Cilnidipine results in vasodilation of both pre and post-capillary resistance vessels, and as well brings down the capillary hypertension and hyper-filtration of fluid into inter-spatial specs. Shetty, et al. (2013) conducted a prospective, observational study to determine cilnidipine can resolve amlodipine-induced pedal edema, Cilnidipine therapy showed complete resolution amlodipine-induced pedal edema. The dual mechanisms of Cilnidipine can lead to complete resolution of amlodipine-induced pedal edema and better hypertension control over amlodipine therapy.

CONCLUSION

Cilnidipine therapy lead to a complete resolution of amlodipine-induced edema along with better hypertension control. Cilnidipine decreases the release of catecholamine by inhibiting N-type of calcium channel at the neuronal terminal. Cilnidipine is a suitable alternative antihypertensive medication for patients with the amlodipine-induced edema.

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Abbreviations:

- AIPE : Amlodipine Induced Pedal Edema
- ACT : After Cilnidipine Treatment
- VMA : Vanillyl Mandelic Acid
- CCB : Calcium Channel Blocker
- BMI : Basal Metabolic Index
- LVF : Left ventricular Ejection Fraction

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