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Original Research Article

Evaluation of Safety and Tolerability of Amlodipine and Cilnidipine - A Comparative Study

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Abstract: Amlodipine and Cilnidipine are found equally efficacious in terms of blood pressure control but very few studies have been conducted on safety and tolerability profile of both the drugs except regarding ankle oedema. Cilnidipine has a slow-onset but the long-lasting antihypertensive action action like Amlodipine. It had get approval in June 2007 and introduced in the market and claimed to be superior over Amlodipine. The aim of this study is to assessment of safety and tolerability of both calcium antagonists i. e Amlodipine and Cilnidipine. The Objectives are to evaluate the incidence of adverse drug reactions of Amlodipine and Cilnidipine and to compare the incidence of ADRs between Amlodipine and Cilnidipine. Patients with hypertension (n= 326) meeting the inclusion and exclusion criteria, reporting in the department of medicine between December 14 to November 15 for their treatment were enrolled in the study. The enrolled patients were then divided as (1) Hypertensive patient - the study group received Cilnidipine and control group receiving Amlodipine. (2) Hypertensive with controlled diabetic patients are also grouped separately as study or control group receiving Cilnidipine or Amlodipine respectively. All patients were examined periodically at 1, 3, 6, and 12 months intervals. Dose of Amlodipine and Cilnidipine were titrated according to their BP goal. We exclude the data of drop out participants, those who withdraw consentand any protocol violation like those patients for whom additional anti hypertensive were added other than ARB or ACEI for inadequate BP control.After exclusion of dropouts, the study was continued in 258 participants. All values were expressed as means ± SEM (n = 6 in each group). The comparison between Amlodipine and Cilnidipine in both diabetic as well as non diabetic hypertensive patients was done by Fischer exact test. Significance is set at $P \leq 0.05$. It is evident from the present study that incidence of ankle edema, palpitations and weight gain was significantly more in Amlodipine than cilnidipine. Incidence of other adverse drug reactions were noted to be more frequent in Amlodipine treated patients but no significant difference was found. It can be concluded that Cilnidipine has a better tolerability profile than Amlodipine, though having equal potency in equivalent doses as the incidence of ADRs were more associated with Amlodipine than Cilnidipine in both diabetic and non diabetic hypertensive patients.

Keywords: Amlodipine, Cilnidipine, Safety, Tolerability, Adverse drug reactions (ADR), Ankle oedema.

INTRODUCTION

Adverse drug reactions are considered to be one of the leading cause of morbidity and mortality and ADRs related hospitalisation, has increased in faster rate in recent times. Although prescription drugs are subject to extensive premarket safety testing prior to approval, all adverse drug reactions (ADRs) are not identified in preclinical and clinical testing and may become apparent after their introduction into the marketplace and their subsequent use within the general population i. e during post marketing surveillance [1]. Number of drugs including antihypertensive medicine have been withdrawn from market and banned due to safety concern like Mibefradil. Around 6% of hospital admissions are estimated to be due to ADRs and about 6-15% of hospitalized patients experience a serious ADR [2].

According to the World Health Organization (WHO) definition, an adverse drug reaction (ADR) is 'a response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function [3].

Hypertension is the medical condition where the systolic blood pressure is more than 140 mm Hg and the diastolic blood pressure is more than 90 mm Hg. It is a chronic disease which is considered to be one of the major public health problems and a significant cardiovascular risk factor. According to the World Health Organization (WHO), each year, at least 7.1 million people die as a result of increased blood pressure [4]. For the treatment of hypertension, a broad range of antihypertensive medications are currently available. Antihypertensive drugs are frequently associated with adverse drug reactions (ADRs) that may limit treatment options and reduce patient adherence, which may hinder blood pressure control. These drugs are believed to cause ADRs or symptoms that make patients feel worse than they did before beginning drug therapy for their "asymptomatic" disease [5]. It is estimated that the prevalence of hypertension in India is about 25% among urban adults and 10% in the rural areas. The lifetime risk of developing hypertension is estimated to be 90% [6].

Dihydropyridine calcium channel blockers comprise a class of powerful, well-tolerated, and safe antihypertensive agents that are widely used either alone or as a key component of combination therapy for hypertension [7]. As per 2007 AHA guidelines, Calcium channel blockers are one of the first line drugs in uncomplicated hypertension [8]. According to JNC VIII guideline calcium channel blockers are first line of treatment in both general black or non black population (including those with diabetes). Amongst which, Amlodipine is a L type calcium channel blocker belonging to third generation of calcium antagonists while Cilnidipine belongs to fourth generation having inhibitory actions on both vascular L type and N type sympathetic calcium channels [9], are commonly used CCB. Both of these drugs are found equally efficacious in terms of blood pressure control [10-12] but very few studies have been conducted on safety and tolerability profile of both the drugs except regarding ankle oedema. Cilnidipine has a slow-onset but the long-lasting antihypertensive action action [13] like Amlodipine [14]. It had get approval in June 2007 and introduced in the market and claimed to be superior over Amlodipine.

AIM

Assessment of safety and tolerability of both calcium antagonists i. e Amlodipine and Cilnidipine

OBJECTIVES

- To evaluate the incidence of adverse drug reactions of Amlodipine and Cilnidipine
- To compare the incidence of ADRs between Amlodipine and Cilnidipine

MATERIALS AND METHODS

Inclusion criteria

- Age : >40 yrs <60 yrs ; BMI >18.5 <30 kg/mtr2 (normal and pre-obese)
- Sex : Both sex
- Patients with Essential hypertension of mild to moderate cases (stage I & stage II) according to JNC 7 (those SBP < 180 and DBP < 110)
- Phase of microalbuminuria. (Spot urinary albumin creatine ratio ACR < 300 mg/gm)
- Hypertensive patients on Amlodipine (2.5 to 10 mg) & Cilnidipine (5 to 20 mg). Or combination with ARB or ACE I.
- Controlled diabetic patient.

Exclusion criteria

- Age : <40 yrs >60 yrs ; BMI <18.5 to >29.99 kg/sq. mtr
- All cases of hypertension with SBP $\geq$ 180 and DBP $\geq$ 110.
- Patients of secondary hypertension or taking antihypertensive medicine other than additional ACEI / ARB.
- Uncontrolled diabetes (HBA1c >7).
- Dyslipidaemic patients on hypolipidaemic medicine.
- Serum creatinine >1.2
- Patient with liver disease
- ACR > 300mg/gm (Spot urine)
- Patients on Pioglitazone
- Patients with heart failure, heart block, aortic stenosis.
- On NSAID for long term; corticosteroid and sex steroids.
- Any other chronic illness (RA, TB, PEM)
- Alcoholic, Hypothyroid, varicose vein.

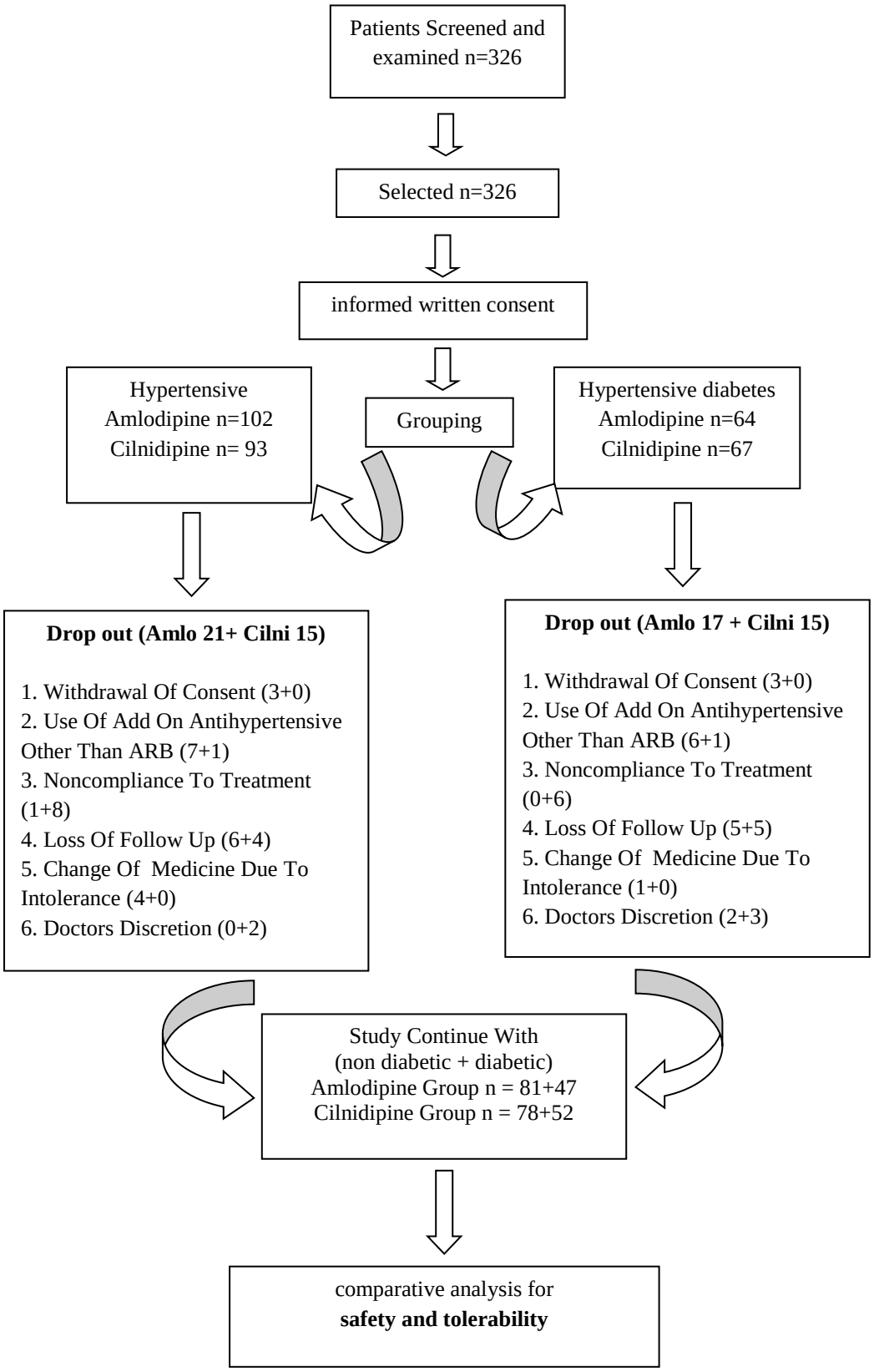
Patient Recruitment

Patients with hypertension meeting the above criteria, reporting in the department of medicine between December 14 to November 16 for their treatment enrolled in study. The study was explained to them in local language and written informed consent was obtained, selected patients were randomized by simple random sampling technique into groups receive either Amlodipine (5 to 10mg) or cilnidipine (10 to 20 mg).

Grouping

The enrolled patients were then divided as (1) Hypertensive patient - the study group received

Cilnidipine and control group receiving Amlodipine. (2) Hypertensive with controlled diabetic patients are also grouped separately as study or control group receiving Cilnidipine or Amlodipine respectively. The grouping is depicted by the flow chart below.



Study setting / location

The study was carried out over two years period (December 14 to November 16). The protocol was approved by the Institutional Human Ethics committee. The study protocol and informed consent was evaluated by the members and necessary changes was incorporated before starting the experiment. The study was conducted in the department of pharmacology in collaboration with medicine department of Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha.

Parameters assessed

1. Baseline monitoring

- Demographic parameters - (Age, sex, weight, height, BMI, Waist circumference)
- Thorough present, past and drug history was taken
- Clinical parameters - Routine baseline values blood pressure, heart rate, clinical examination.
- Biochemical parameters - Lipid profile (serum cholesterol , triglycerides , LDL, HDL , VLDL), Serum creatinine , urea, potassium , FBS & HBA1C, Spot urine albumin/ creatinine ratio.
- ECG & ECHO
- USG with Doppler whole abdomen.
- TSH, T3 and T4.

2. Periodically monitoring

Following parameters will be checked periodically i.e. on initiation, and then follow up after 14 days, 1m, 3m, 6m, & 12m.

- Proper history and evaluation of any adverse drug reaction
- Clinical parameters - Blood pressure, heart rate, clinical examination in every visits.
- Biochemical parameters - Lipid profile (serum cholesterol , triglycerides , LDL , HDL , VLDL), Serum creatinine , urea, FBS & HBA1C , Spot urine albumin/ creatinine ratio on 3m, 6m, 12m.
- ECG & ECHO at 12 months.

3. Clinical evaluation of ankle oedema

- Since the assessment of ankle oedema in OPD by clinical examination as discussed below is most feasible and also reliable than other methods used for measure ankle oedema this method was chosen.
- Ankle oedema is clinically evaluated by applying pressure over a bony prominence (proximal to lateral or medial malleoli). To provide effective compression finger pressure (right thumb) should be maintained for 20 to 30 second and evaluate pitting and time taking for rebound or disappear [15].

Patients were instructed to attend the hypertension clinic immediately in case of any adverse event, along with advice for salt restriction (no added salt) and regular physical activity. Adherence was monitored by pill count. All patients are examined periodically at intervals stated above. Dose of Amlodipine and Cilnidipine are titrated according to their BP goal. We exclude the data of drop out participants, those who withdraw consent, intolerable adverse drug reaction and any protocol violation like those patients for whom additional anti hypertensive were added other than ARB or ACEI for inadequate BP control.

RESULTS AND ANALYSIS

Incidence rates of adverse reaction of Clnidipine and the Amlodipine group were recorded in all patients. The outcomes of present study demonstrated that there were statistically significant difference in adverse drug events between Cilnidipine and Amlodipine group in three respect i.e. ankle oedema, weight gain and palpitation, with higher incidence in Amlodipine than that of Cilnidipine. Other observed minor adverse reactions for Cilnidipine included headache (5.13% in DM(-); 3.85% in DM(+)), dizziness (3.85% in each DM(-) & DM(+)), and facial flushing (3.85% in DM(-) and 7.69% in DM(+)). The frequently observed adverse reactions of the Amlodipine treated group were headache (6.17% in DM(-) and 4.26 % in DM(+)), dizziness (8.64% in DM(-) and 12.77% in DM(+)) and gastrointestinal symptoms (7.41% in DM(-) and 25.53% in DM(+)). Unlike in SAKURA Trial severe adverse drug event like Stroke; Myocardial Infarction; Carcinoma; Acute pancreatitis; Interstitial pneumonia was not seen in any study participant. Concerning all non-severe adverse event during whole study period, present study showed that Cilnidipine is more well tolerable than Amlodipine in both DM(-) (Incidence of ADE by Amlodipine 81.25% vs. Cilnidipine 18.75%) and DM(+) (Incidence of ADE by Amlodipine 72.55% vs. Cilnidipine 27.45%) patients. A recent meta-analysis on the efficacy and safety of Cilnidipine has demonstrated good tolerability and an antihypertensive efficacy equivalent to amlodipine [16]. In diabetic patients, the relative risk of adverse events associated with the use of CCBs is greater [17], results of present study is corroborative with this result (in non-diabetic patients average 0.6 event per patients vs. diabetic 1 event per patient, taking in to account all incidence of ADE by Amlodipine and Cilnidipine).

Table 1: Showing comparison between amlodipine and cilnidipine regarding frequency of adverse drug reactions (non severe)

DATA ANALYSED NAME OF ADR	Hypertensive Patients (Amlodipine N 81) + (Cilnidipine N 78)			Diabetic Hypertensive Patients (Amlodipine N 47) + (Cilnidipine N 52)		
	Amlodipine	Cilnidipine	P Value	Amlodipine	Cilnidipine	P Value
Ankle Oedema**	21[¥] (25.93%) M 10 / F 11 P 0.191 NS + ARB 2 / - ARB 19 P 0.025 S	2 (2.56%) M 0 / F 2 P 0.176 NS + ARB 0 / - ARB 2 P 1.000 NS	0.0001 s	11[¤] (23.4%) M 4 / F 7 P 0.0765NS + ARB 2 / - ARB 9 P 0.041 S	1 (1.92%) M 0 / F 1 P 0.404 NS + ARB 0 / - ARB 1 P 1.000NS	0.0013 S
Flushing	5 (6.17%)	2 (2.56%)	0.443 NS	4 (8.51%)	1 (1.92%)	0.188 NS
Palpitation	15 (18.52%)	0	0.0001S	11 (23.4%)	3 (5.77%)	0.0189S
Headache	5 (6.17%)	4 (5.13%)	1.000NS	3 (6.38%)	3 (5.77%)	1.000NS
Nausea	0	0		0	0	
Fatigue / Asthenia	3 (3.7%)	3 (3.85%)	1.000NS	6 (12.77%)	4 (7.69%)	0.511NS
Constipation	6 (7.41%)	2 (2.56%)	0.277 NS	12 (25.53%)	5 (9.62%)	0.060 NS
Dizziness	7 [£] (8.64%)	3 (3.85%)	0.328 NS	9 (19.15%)	6 (11.54%)	0.401NS
Shortness Of Breath	0	0		0	0	
Excessive Hypotension	2 (2.46%)	0	0.497NS	2 (4.26%)	0	0.223 NS
Gum Hypertrophy	0	0		1 (2.13%)	0	0.475 NS
Wt Gain	14 (13.48%)	2 (2.56%)	0.0027 S	15 (31.9%)	5 (9.62%)	0.011 S
Cough	0	0		0	0	
No Of Adverse Drug Events	Amlodipine 78 (81.25%) Cilnidipine 18 (18.75%) Total 96			Amlodipine 74 (72.55%) Cilnidipine 28 (27.45%) Total 102		
Facial* Telangiectasia	1	0		0	0	

* This Patient Was Excluded From Study Due To Intolerance.
** 4 Out Of 5 Patients On Amlodipine 10 Mg Develop Ankle Oedema, Though All Of Them Were On ARB.
¥ 2 Female Patients Were Excluded Due To Intolerable Ankle Oedema At 6 Months
¤ 1 Female Patients Were Excluded Due To Intolerable Ankle Oedema At 6 Months
£ 1 Male Was Excluded Due To Recurrent Episode Of Orthostatic Hypotension
+ARB- Patients on Amlodipine or Cilnidipine plus Angiotensin receptor blockade
-ARB- Patients on Amlodipine or Cilnidipine without Angiotensin receptor blockade

DISCUSSION

It was obvious in this study that Amlodipine treatment produced more significantly ankle oedema than Cilnidipine ($p < 0.0001$ in DM(-); p 0.0013 in DM(+)). In present study, incidence of ankle oedema was 25.93% in DM(-) and 23.4% in DM(+) patients, whereas with Cilnidipine it was 2.56% and 1.92% respectively. Incidence of ankle oedema with Amlodipine has been found to be between 1.7% up to 32% in different clinical studies [18] which coincides with present study.

Following is the postulated mechanism for CCB induced ankle oedema:

1. In normal individual pre capillary vasoconstriction in response to venous congestion protects the capillary bed from increased blood pressure, thus restricts hydrostatic filtration of fluid into the interstitium. L-type CCBs like Amlodipine directly inhibit pre-capillary constriction and causes arteriolar dilatations and thus leads to intestinal oedema [19].
2. Capillary hypertension due to dilatation of pre-capillary resistance vessels by L-type CCBs sparing post capillary vascular tone leading to capillary hypertension and promotes fluid filtration into the interstitium [20].
3. Increased micro vascular permeability which causes extravasations of plasma protein and water into the interstitial space [21, 22].

This oedema is not relieved by diuretics, but can be reduced to some extent with ACE inhibitors and ARBs, which proves the fact that oedema with Amlodipine is not the result of fluid retention [23-26]. In fact, a decrease in the frequency of pedal oedema due to L-type calcium blockers is reported when these drugs are combined with ACEI/ARB, which have a vasodilatory effect on the venules [27]. Similarly in present study significantly less frequency of ankle oedema with concomitant ARB is also seen in Amlodipine treated arm (p 0.0252 in DM(-) ; p 0.0410 in DM(+)). On the other hand when ARB was added with Cilnidipine, no significant change in frequency noted (p 1.0000 in both DM(-) and DM(+)). This was due to dual blockage of L –type and N-type Ca $^{++}$ Channels by Cilnidipine. L-type CA ++ channel blockade inhibits pre-capillary vasoconstriction leading vasodilatation such as Amlodipine [28]. N-type Ca^{++} channel blockade disrupts outflow of sympathetic nervous system, leading to further vasodilatation by lowering plasma catecholamine. Sympathetic nerves are found in the venules, so drugs that block N-type calcium channels possibly cause venodilation [29]. This twin action result vasodilatation of both pre & post capillary resistance vessels and prevent hyperfiltration of fluid into the interstitium [30]. So additional advantage of venodilatation by ARB was not prominant when used with Cilnidipine in contrast to Amlodipine.

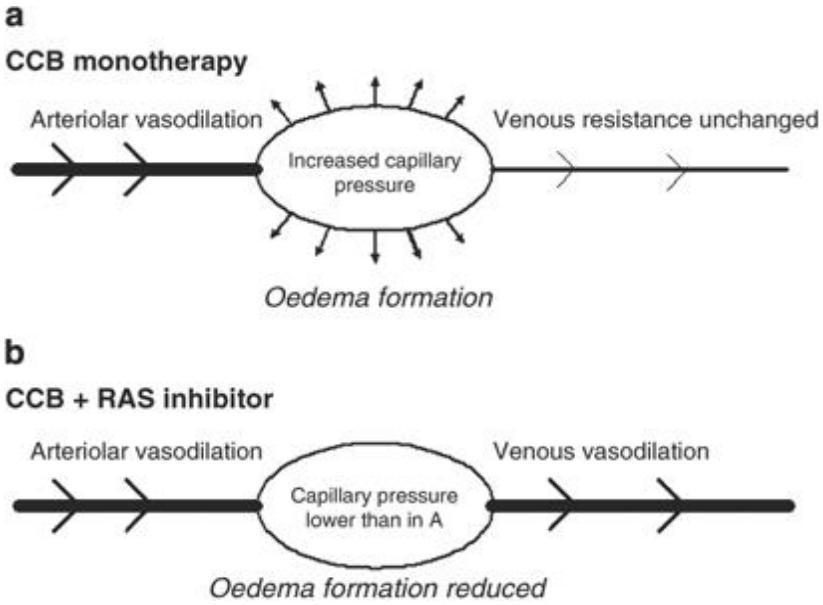


Fig-1: Effects of calcium channel blockers (CCBs, administered with and without a renin-angiotensin system (RAS) inhibitor, on capillary pressure and oedema formation. (a) CCB monotherapy; (b) CCB+RAS inhibitor

Dihydropyridine CCBs cause selective vasodilatation of the arteriolar side of the circulation. Administration of CCBs as monotherapy causes increased pressure within the capillary bed, leading to fluid transudation and oedema formation. Inhibitors of the RAS, that is, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) cause both arteriolar and venous vasodilation. Addition of an ACEI or an ARB to a regimen of CCB monotherapy reduces the pressure within the capillary bed, thereby ameliorating the oedema.

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 oedema, compared with the other CCBs which act only on L-type calcium channels.

Adake P *et al*. showed that both Amlodipine and Cilnidipine have equal blood pressure lowering efficacy but Cilnidipine being N type and L type CCB, associated with lower incidence of pedal oedema compared to only L type channel blocked by Amlodipine [31], coincides with this study. Our previous study also concluded that Cilnidipine being N-type and L-type CCB, associated with much lower incidence of pedal oedema compared to only L-type channel blocker racemic Amlodipine [32]. Shetty R *et al.,* Sarkar NC *et al*. and Prasad RS demonstrated that therapy with Cilnidipine results in complete resolution of Amlodipine-induced oedema in all the cases without significant worsening of hypertension or tachycardia [3, 33, 34]. According to Neki NS et al. unlike Amlodipine, Cilnidipine rarely cause ankle oedema [35], coincides with the present study. Karch FE *et al.* showed that Amlodipine induced ankle oedema was 17% in their study [36] whereas in this study, the incidence was 25% approximately**.**

The risk of developing ankle oedema while using CCB therapy appears to be higher in women, older patients, those with heart failure, upright postures,

and those in warm environments [37, 38]. In present study it was also seen that female are more prone to ankle oedema for all type of CCB but without statically significance for both Amlodipine (p 0.1914 DM(-); p 0.0765 DM(+)) and Cilnidipine (p 0.1758 DM(-); p 0.4038 DM(+)). In other supportive publications, incidence rate of ankle oedema with DHP CCBs was seen especially in women, and this oedema was frequently dose related [39, 40]. Similarly present study showed that 4 out of 5 patients on Amlodipine 10 mg develop ankle oedema, though all of them were on ARB. The exact cause of more ankle oedema in female is unclear but it may be due to more self-examination, intolerance to cosmetic problem or due to associated idiopathic oedema (also known as cyclical oedema, periodic oedema and the fluid retention syndrome). It is a poorly understood syndrome occurring almost exclusively in women. It is characterized by complaints of intermittent swelling of the face, trunk and limbs and by weight variation unrelated to the menstrual cycle. There is evidence of increased capillary permeability in idiopathic oedema which leads to extravasations of fluid from the vascular compartment in the upright posture with secondary retention of sodium and water through the renin-angiotensin-aldosterone pathway [41-43]. No differences were found in the results obtained in the follicular and luteal phases of the menstrual cycle or in the pre- and post-menopausal patients [44]. Present study also showed that female are more prone to ankle oedema but there is no statistical significance.

Regarding palpitation, frequency of complain wass significantly more in Amlodipine than Cilnidipine treated patients in both DM(-) ($p < 0.0001$) and DM(+) (p 0.0189) patients. As stated previously clinically Sakata *et al.* demonstrated by using 123I-metaiodobenzylguanidine cardiac imaging that Cilnidipine suppressed cardiac sympathetic over activity while Amlodipine had little suppressive effect [45]. Attenuating norepinephrine release from the sympathetic nerve endings by blocking the N-type calcium channels with Cilnidipine might cause a decrease in PR. In present study, the incidence of palpitation is more is diabetic than non-diabetic patients, may be due to cardiac autonomic neuropathy in diabetes [46]**.**

Constipation as a result of some calcium channel blockers may be caused by inhibition of colonic motor activity [47]. In present study, though no significant difference seen between Amlodipine and Cilnidipine in respect to constipation (p 0.2772 in DM(-)) ; 0.598 in DM(+)) but Amlodipine had apparently higher incidence of constipation. The incidence is more in diabetic patients than nondiabetic patients for both drug. This may be due to autonomic gastroparesis by diabetes. According to Koçkar MC *et al.* gastroparesis is a frequent complication of diabetes mellitus and autonomic neuropathy seems to be one of the most important mechanisms underlying this entity [48].

Flushing is a common side effect, caused by vasodilatation. Regardless of cause they share a common pathway in release of vasoactive mediators [49] (arachidonic acid , prostaglandin D2, and endogenous catacholamine.). The CCBs that may elicit this reaction in order of frequency are Amlodipine 1.2-2 percent [50] , Cilnidipine 4.5 percent [51] corroborative with present study. More flushing in Cilnidipine group may be due to N type CCB and thereby inhibition of release of noradrenaline an endogenous catecholamine.

Regarding gingival hyperplasia the prevalence of overgrowth with the use of CCBs may be as high as 38 percent [52], the incidence is 3.3-times more common in men than in women [53]. Young *et al.* and Vlenten V *et al.,* proposed that inflammation and gingivitis secondary to bacterial plaque induce the production of gingival crevicular fluid [54, 55]. This serum-derived transudate may cause accumulation of the CCB in the gingivae with subsequent localized toxic effect and gingival hyperplasia. Only one diabetic patient with Amlodipine developed mild gingival hyperplasia at the end of 12 months of treatment.

Photodistributed facial telangiectasia has been described for amlodipine [56-58], clinically it is characterized by marked arborizing telangiectasia spreading on all the photoexposed areas of the body more frequently at face . The aetiology of this disorder is not fully understood. One of the several mechanisms that have been postulated both the vasodilatory action of the CCB and the actinic damage produced in the vessels in photoexposed areas may contribute to this phenomenon [59]. Only one non diabetic patient with Amlodipine developed facial telangiectasia, and was excluded from study after consulting with dermatology department.

Regarding headache the incidence is nearly same for Amlodipine (3.1%) and Cilnidipine (3.29%) as shown in a meta-analysis [60] by Guo-liang X *et al.* Present study also shows no significant difference between both drugs. But in present study, the incidence rate of headache is high in Amlodipine group. M R Law *et al.* showed headache by CCB is dose dependent [61]. This dose dependent effect was also seen in present study. Every one of the patients who were on Amlodipine 10 mg or Cilnidipine 20 mg, had the grumble of head ach.

Weight gain was another frequent complaint seen in the present study with those patients had ankle oedema. This may be due to fluid transudation caused by CCBs as discussed above. It was observed to be significantly more with Amlodipine treated arm (p

0.0027 in DM(-) ; p <0.0001 in DM(+)) in both diabetic and non-diabetic patients. In the present study, complain of weight gain was relatively more from diabetic patients in both with Amlodipine or Cilnidipine group. This may be due to use of OHA. Weight gain, which is typically 1–4 kg, is another concern of sulfonylurea therapy, particularly given that many Type 2 diabetes patients are already overweight or obese [62, 63].

The meta analysis by Guo-liang X *et al*. observed that the incidence of dizziness [60] with Cilnidipine use was 4.61% while that of Amlodipine group was 6.65% without any statistical significance which further coincides with present study (Amlodipine 8.64% vs. Cilnidipine 3.85% : p = 0.3278 in DM(-) ; Amlodipine 19.15% vs. Cilnidipine 11.54% : p = 0.4014 in DM(+) group). The incidence of episode of dizziness is more in Amlodipine group of patients than Cilnidipine. Present study showed frequency of dizziness more in diabetic patients than non-diabetic patients, may be due to associated cardiac autonomic neuropathy in diabetes [64] and thereby increase chance of orthostatic hypotension [46]**.** Diabetes was found to be independently associated with orthostatic hypotension [65]. In this study, all the dizziness episodes were seen in patients around 55 to 60 year of age group of either sex. In a population studies with calcium channel blockers, orthostatic hypotension shows a 2-to-5-times increase in prevalence during treatment with these drugs, especially in elderly population [66-68], while there is no association between the use of calcium channel blockers and orthostatic hypotension in diabetes [69, 70]. Tatsuya Kai *et al*. concluded that with Cilnidipine no orthostatic hypotension was observed during the head-up tilt test [71].

The exact cause of fatigue and asthenia caused by CCB is not known. Present study showed no significant difference between Amlodipine and Cilnidipine in this regard (p 1.000 in DM(-) ; p 0.5111 in DM(+) patients). But it was obvious from our results that incidence of fatigue was more in diabetic patients than non-diabetic patients which could be due to associated diabetes. According to Fritschi C *et al*, fatigue in diabetes is likely caused from the interplay of physiological, psychological, and lifestyle-related factors [72].

CONCLUSION

The present study reveals that Amlodipine and Cilnidipine are safer antihypertensive agents with very less of any severe adverse effects which could be life threatening. Incidence of ADRs were more associated with Amlodipine than Cilnidipine in both diabetic and non diabetic hypertensive patients and hence it can be concluded that Cilnidipine has a better tolerability profile than Amlodipine though having equal potency in equivalent doses.

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REFERENCES

1. The clinical impact of adverse event reporting-A med watch continuing education article. Provided as a service by the Staff College, Center for Drug Evaluation and Research, Food and Drug Administration October 1996, available from-http://www.fda.gov/downloads/safety/medwatch/ucm168505.pdf.
2. Riley J, Wilton LV, Shakir SA; A post marketing observational study to assess the safety of mibefradil in the community of England. Int J Clin Pharmacol Ther., 2002; 40:241–8.
3. Tech Rep Ser WHO, No. 498. Geneva: WHO; World Health Organization International drug monitoring: The role of national centers, 1972.
4. Aellig HW; Adverse reactions to World Health Organization Preventing Chronic Diseases: A Vital Investment. Geneva, Switzerland: WHO; 2005.
5. Raghu Kumar V, Raghu Ram V, Guru Prasad B, Mohanta GP, Manna PK; A study of adverse drug reactions due to antihypertensive drugs in a tertiary care teaching hospital; Int. J. of Pharm. & Life Sci. (IJPLS), 2011; 25: 767-772.
6. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB; Residual life-timerisk for developing hypertension in middle-agedwomen and men : The framingham Heart study. JAMA, 2002; 287: 1003-10.
7. Lang R, Steffen HM, Kaufmann W; Traditions of antihypertensive therapy in different countries–continental Europe. In: Ganten D, Mulrow PJ; Handbook of Experimental Pharmacology, Springer, Berlin-Heidelberg New York, 1990; 811–9.
8. Saseen JJ; Hypertension, Applied therapeutics, The clinical use of drugs . Mary Anne Koda-Kimble, Lloyd Yee Young, Brian K; Alldredge , 9th edition, Lippincott Williams & Wilkins, 2009; 13-8.
9. Zaman ZA, Kumari V; Comparison of the effects of amlodipine and cilnidipine on blood pressure, heart rate, proteinuria and lipid profile in

hypertensive patients. Int J Basic Clin Pharmacol., 2013; 2(2); 160-164.
10. Hoshide S, Kario K, Ishikawa J, Eguchi K, Shimada K; Comparison of the effects of cilnidipine and amlodipine on ambulatory blood pressure. Hypertens Res., 2005; 28 (12):1003-1008.
11. Kanaoka T, Tamura K, Wakui H, Ohsawa M, Azushima K, Uneda K, Kobayashi R; L/N-Type Calcium Channel Blocker Cilnidipine Added to Renin-Angiotensin Inhibition Improves Ambulatory Blood Pressure Profile and Suppresses Cardiac Hypertrophy in Hypertension with Chronic Kidney Disease. Int. J. Mol. Sci., 2013; 14: 16866-16881.
12. Ando K, Ueshima K, Tanaka S, Kosugi S, Sato T, Matsuoka H, Nakao K, Fujita T; Comparison of the Antialbuminuric Effects of L-/N-type and L-type Calcium Channel Blockers in Hypertensive Patients with Diabetes and Microalbuminuria: The Study of Assessment for Kidney Function by Urinary Microalbumin in Randomized (SAKURA) Trial. Int. J. Med. Sci., 2013; 10:1209-16.
13. Ozawa Y, Hayashi K, Kobori H; New generation calcium channel blockers in hypertensive treatment.Curr Hypertens Rev., 2006; 2:103–11.
14. Faulkner JK, McGibney D, Chasseaud LF, Perry JL, Taylor IW; The pharmacokinetics of amlodipine in healthy volunteers after single intravenous and oral doses and after 14 repeated oral doses given once daily. Br J Clin Pharmacol., 1986; 22: 21−25.
15. Hutchison; oedema. In Michael Swash MG, editor. Hutchinson's clinical methods. 22nd ed. London: Saunders(W.B) Co Ltd., 2006; 76:255.
16. Xu G, Wu H, Du B, Qin L; The efficacy and safety of cilnidipne on mild to moderate essential hypertension: A systematic review and meta-analysis of randomized controlled trials in Chinese patients. Cardiovasc Hematol Disord Drug Targets, 2012; 12: 56-62.
17. Pahor M, Kritchevsky S, Zuccala G, Guralnik J; Diabetes and Risk Of adverse events with calcium antagonists. Diabetes Care, 1998; 21(1):193-4, 1998.
18. Patil PA, Kothekar MA; Development of safer molecules through chirality. Indian J Med Sci., 2006; 60:427–37.
19. Pedrinelli R, Dell'Omo G, Mariani M; Calcium channel blockers, postural vasoconstriction and dependent oedema in essential hypertension. J Hum Hypertens., 2001; 15: 455-61.
20. Gustafsson D, Lanne T, Bjerkhoel P, Johansson P, Lundvall J; Microvascular effects and oedema formation of felodipine in man. J Hyprtens Suppl., 1989; 7: S161-7.
21. Valentin JP, Ribstein J, Halimi JM, Mimran A; Effect of different calcium antagonists on transcapillary fluid shift. Am J Hypertens., 1990; 3: 491-5.
22. Hulthen UL, Cao Z, Rumble JR, Cooper ME, Johnston CI; Vascular hypertrophy and albumin permeability in a rat model combining hypertension and diabetes mellitus. Effects of calciumantagonism, angiotensin converting enzyme inhibition, and angiotensin II-AT1-receptor blockade. Am J Hypertens., 1996; 9: 895-901.
23. Thacker HP; S-amlodipine - The 2007 Clinical Review, J Indian Med Assoc., 2007; 105: 180-90.
24. Fogari R, Malamani GD, Zoppi A, Mugellini A, Rinaldi A, Vanasia A, Preti P; Effect of benazepril addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. Journal of human hypertension, 2003; 17(3):207-12.
25. Weir MR, Rosenberger C, Fink JC; Pilot study to evaluate a water displacement technique to compare effects of diuretics and ACE inhibitors to alleviate lower extremity edema due to dihydropyridine calcium antagonists. Am J Hypertens., 2001; 14:963-968.
26. Fogari R, Malamani G, Corradi L, Mugellini A, Preti P, Zoppi A, Derosa G; Effect of valsartan or olmesartan addition to amlodipine on ankle edema in hypertensive patients. Advances in therapy, 2010; 27(1):48-55.
27. Pedrinelli R, Dell′Omo G, Melillo E, Mariani M; Amlodipine, enalapril, and dependent leg edema in essential hypertension. Hypertension., 2000; 35:621-5.
28. Uneyama H, Uchida H, Konda T, Yoshimoto R; Cilnidipine: Preclinical profile and clinical evaluation. Cardiovasc Drug Rev., 1999; 17: 341-57
29. Smyth L, Bobalova J, Ward SM, Keef KD, Mutafova-Yambolieva VN; Cotransmission from sympathetic vasoconstrictor neurons: Differences in guinea-pig mesenteric artery and vein. Auton Neurosci., 2000; 86:18-29.
30. Fujita T, Ando K, Nishimura H, Ideura T, Yasuda G, Isshiki M, Takahashi K; Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. (CARTER Trial) Kidney Int., 2007; 72: 1543–1549.
31. Adake P, Somashekar HS, Mohammed Rafeeq PK, Umar D, Basheer B, and Baroudi K; Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study. J Adv Pharm Technol Res., 2015; 6(2): 81–85.
32. Mohanty M, Tripathy KP, Sarkar S, Srivastava V; Comparative Analysis On Incidence Of Pedal Oedema Between Amlodipine, Cilnidipine And S-Amlodipine In Mild To Moderate Hypertensive

Individuals Of Either Sex. IOSR-JDMS,2016; 15(3): 24-34.
33. Shetty R, Vivek G, Naha K, Tumkur A, Raj A, Bairy KL; Excellent Tolerance to Cilnidipine in Hypertensives with Amlodipine - Induced Edema; N Am J Med Sci., 2013; 5(1): 47–50.
34. Prasad RS. Replacement of Amlodipine with Cilnidipine and assessment of pedal edema along with blood pressure control. Sch. J. App. Med. Sci., 2015; 3(4A):1680-1682.
35. Neki NS, Jain A; Cilnidipine induced ankle edema: a rare adverse event. J Pioneer Med Sci., 2016; 6(1): 14-15 .
36. Karch FE, Pordy R ,Benz JR, Carr A, Lunde NM, Marbury T, Tarro JN; Comparative efficacy and tolerability of two long-acting calcium antagonists, mibefradil and amlodipine, in essential hypertension. Clinical Therapeutics, 1997; 19(6): 1368–1378.
37. Sica DA; Calcium channel blocker-related peripheral edema: can it be resolved? Journal of Clinical Hypertension, 2003; 5(4):291-97.
38. Lund-Johansen P, Stranden E, Helberg S, Wessel-Aas T, Risberg K, Rønnevik PK, Istad H, Madsbu S; Quantification of leg oedema in postmenopausal hypertensive patients treated with lercanidipine or amlodipine. Journal of hypertension, 2003; 21(5):1003-10.
39. Steffen HM; Amlodipine—a third generation dihydropyridine calcium antagonist. J Clin Basic Cardiol., 1999; 2:45–52.
40. Langdon C; Treatment of hypertension in patients ≥ 65 years of age: experience with amlodipine. Clin Ther., 2000; 22:1473–1482.
41. Thorn GW; Approach to the patient with 'idiopathic oedema' or' periodic swelling'. JAMA, 1968; 206: 333-338.
42. Edwards OM, Bayliss NIS; Idiopathic oedema of women. A clinical and investigative study. Q J Med., 1976; 45: 125-144.
43. Dunnigan MG; The recognition and management of the fluid retention (idiopathic or cyclical oedema) and premenstrual syndromes. In: McNaughton, C. (ed) Medical Gynaecology. Blackwell Scientific Publications, Oxford. 1985; 27-54.
44. Edwards OM, Bayliss RI; Idiopathic oedema of women: a clinical and investigative study. QJM, 1976; 45(1):125-44.
45. Sakata K, Shirotani M, Yoshida H, Nawada R, Obayashi K, Togi K, Miho N; Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. Hypertension, 1999; 33(6):1447-52.
46. Busui RP; Cardiac Autonomic Neuropathy in Diabetes; Diabetes Care, 2010; 33(2): 434–441.
47. Bassotti G, Calcara C, Annese V, Fiorella S, Roselli P, Morelli A; Nifedipine and verapamil inhibit the sigmoid colon myoelectric response to eating in healthy volunteers. Dis Colon Rectum, 1998; 41(3):377-80.
48. Koçkar MC, Kayahan IK, Bavbek N; Diabetic gastroparesis in association with autonomic neuropathy and microvasculopathy. Acta Med Okayama, 2002; 56(5):237-43.
49. Joseph C; English III, A.C.H.T.J.p.L.M.G., ed., Flushing. In Skin and Systemic disease a clinician's guide. Boka Raton: Tailor and Francis group, 2015; 36-37.
50. Osterloh I; The safety of amlodipine, Am Heart J., 1989; 118(5 Pt 2): 1114-9; discussion 1119-20.
51. Saruta T; Current status of calcium antagonists in Japan. Am J Cardiol., 1998; 82:32R-34R.
52. Prisant LM, Herman W; Calcium channel blocker induced gingival over-growth. J Clin Hypertens (Greenwich), 2002; 4(4):310–1.
53. Prisant LM, Herman W; Calcium channel blocker induced gingival overgrowth, J Clin Hypertens (Greenwich); 2002; 4(4):310-1.
54. Verapamil; drug information handbook, UpToDate(r), 2002.
55. van der Vleuten CJ, Trijbels-Smeulders MA, van de Kerkhof PC; Telangiectasia and gingival hyperplasia as side-effects of amlodipine (Norvasc) in a 3-year-old girl, Acta Derm Venereol., 1999; 79(4):323-4.
56. van der Vleuten CJ, Trijbels-Smeulders MA, van de Kerkhof PC;Telangiectasia and gingival hyperplasia as side-effects of amlodipine (Norvasc) in a 3-year-old girl. Acta Derm Venereol., 1999; 79(4):323-4.
57. Basarab T, Yu R, Jones RR, Calcium antagonist-induced photo-exposed telangiectasia, Br J Dermatol.,1997; 136(6):974-5.
58. Grabczynska SA, Cowley N; Amlodipine induced-photosensitivity presenting as telangiectasia, Br J Dermatol., 2000; 142(6):1255-6.
59. Silvestre JF, Albares MP, Carnero L, Botella R; Photodistributed felodipine-induced facial telangiectasia, J Am Acad Dermatol., 2001; 45(2):323-4.
60. Liang XD, Hui X, Hai-di W, Ling Q; A meta-analysis of the efficacy and safety of cilnidipine in Chinese patients with mild to moderate essential hypertension. African Journal of Pharmacy and Pharmacology, 2012; 6(32): 2393-2399.
61. Law MR, Morris JK, and Wald NJ; Calcium channel blockers and headache; Br J Clin Pharmacol., 2007; 63(2): 157–158.
62. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy a consensus statement of the

American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care, 2009; 32(1):193-203.
63. Krentz AJ, Bailey CJ; Oral antidiabetic agents: current role in Type 2 diabetes mellitus. Drugs, 2005; 65(3):385–411.
64. Ewing DJ, Campbell IW, Clarke BF; The natural history of diabetic autonomic neuropathy. Q J Med., 1980; 49: 95–108.
65. Wu JS, Yang YC, Lu FH, Wu CH, Wang RH, Chang CJ; Population-Based Study on the Prevalence and Risk Factors of Orthostatic Hypotension in Subjects With Pre-Diabetes and Diabetes; Diabetes Care, 2009; 32(1): 69–74.
66. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O; Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmö Preventive Project). European heart journal, 2010; 31(1):85-91.
67. Luukinen H, Koski K, Laippala P, Kivela SL; Prognosis of diastolic and systolic orthostatic hypotension in older persons. Arch Intern Med., 1999; 159: 273-280.
68. Fedorowski A, Burri P, Juul-Moller S, Melander O; A dedicated investigation unit improves management of syncopal attacks (Syncope Study of Unselected Population in Malmo--SYSTEMA I). Europace, 2010; 12: 1322-1328.
69. Wu JS, Lu FH, Yang YC, Chang CJ; Postural hypotension and postural dizziness in patients with non-insulin-dependent diabetes. Arch Intern Med., 1999; 159: 1350-1356.
70. Hirai FE, Moss SE, Klein BE, Klein R; Postural blood pressure changes and associated factors in long-term Type 1 diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy. J Diabetes Complications, 2009; 23: 83-88.
71. Kai A, Kuzumoto Y; Effects of a Dual L/N-Type Calcium Channel Blocker Cilnidipine on Blood Pressure, Pulse Rate, and Autonomic Functions in Patients with Mild to Moderate Hypertension; Clinical and Experimental Hypertension, 2009; 31(7): 595-604.
72. Fritschi C, Quinn L; Fatigue in Patients with Diabetes: A Review. J Psychosom Res., 2010; 69(1): 33–41.