

Comparative Analysis On Incidence Of Pedal Oedema Between Amlodipine, Cilnidipine And S-Amlodipine In Mild To Moderate Hypertensive Individuals Of Either Sex.

Prof. Dr Manjushree Mohanty : Prof. Dr K P Tripathy : Dr Sougata Sarkar : Dr Vartika Srivastava

Abstract:

Aim And Objective. 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). It controls hypertension adequately, but very often produces ankle oedema. Our object of study was to compare the incidence of ankle oedema and its variation on the basis of gender, amongst commonly used Dihydropyridine Calcium Channel Blockers like racemic Amlodipine, s Amlodipine, L/N type CCB Cilnidipine in mild to moderate hypertensive patients.

Material And Methods: This was a prospective OPD based study performed on 180 patients between 40 to 60 years, divided into two groups of either sex with 90 each, amongst which, 30 patients were on amlodipine, 30 on s amlodipine and 30 on cilnidipine. Congestive cardiac failure, cirrhosis of the liver, concomitant Nephropathy and secondary hypertension were excluded by clinical examination and appropriate laboratory tests. Clinical assessment of blood pressure, pulse rate, ankle oedema were recorded at the beginning of the study and after one month and three months of therapy.

Result: Twelve weeks follow up of patients revealed adequate blood pressure control with higher incidence of oedema for Amlodipine and lowest incidence for Cilnidipine and much lower incidence for s Amlodipine when compared to Amlodipine. Incidence of oedema is higher in females than males for each drug.

Conclusion: Amlodipine is associated with more incidence of ankle oedema in both sex group than s Amlodipine or Cilnidipine with highly statistical significance. Cilnidipine being N-type and L-type CCB, associated with much lower incidence of pedal edema compared to only L-type channel blocker racemic Amlodipine. The less incidence of ankle edema by s-Amlodipine as showed in this study coincides with the fact that the R-enantiomer component could be the reason for the appearance of edema with racemic Amlodipine. Present study also shows female are more prone to ankle edema than male, but of no statistical significance. Though apparently s Amlodipine is associated with more incidence of oedema than Cilnidipine, but of no statistical significance.

Keywords: Hypertension, Calcium channel blocker (CCB), Amlodipine (L-type CCB), s Amlodipine, Ankle edema, Cilnidipine (L/N type CCB).

I. Introduction

Systemic hypertension is a standout amongst the most well-known diseases of mankind influencing around 20% of populace internationally [1]. All segments of populace in India experience the ill effects of the malady, with higher pervasiveness in urban (30.9%) than the rural populace (21.2%). Majority of the patients suffering from hypertension have no symptoms, however a normal checking of blood pressure ascribes to right on time detection of hypertension [2]. According to 2007 AHA guidelines, Calcium channel blockers are one of the primary line of treatment in uncomplicated hypertension [3]. By JNC VIII rule calcium channel blockers are first line of treatment in both general dark or non dark populace (counting those with diabetes).

Amlodipine, the III generation dihydropyridine contrasts from different DHPs in its pharmacokinetic properties, for example, slow absorption and longer $t_{1/2}$ (40hrs). It produces both peripheral and coronary vasodilatation and less reflex tachycardia. It can be controlled as a helpful single measurement beginning from 2.5mg which can be extended up to 10mg [4]. In spite of the fact that amlodipine is valuable as antihypertensive in numerous grounds, the symptom of ankle edema, however it is self constrained minor impact, but still needs to be discontinued in 9.3% of patients [5].

The doctor typically change/include amlodipine with ACE inhibitors or ARBs or diuretics. Though with the change of amlodipine, the blood pressure control may not be adequate but it resolves the ankle oedema satisfactorily i.e ankle edema resolves at the cost of poor control of blood pressure which is undesirable. Then again add on therapy with amlodipine is not always clinically indicated. Substitution of amlodipine with another CCB might be a superior choice if blood pressure is enough controlled with no ankle edema.

Fundamentally, Amlodipine is a racemic blend of two enantiomers, S and R. Subsequent to amlodipine racemic blend has more special activity over arteriolar smooth muscle than the veins, vessels in feet are

presented to un-physiologically high hydrostatic pressure attributable to pre-capillary dilatation and reflex post capillary constriction, which according to Starling mechanism leads to exudation of fluid [6].

Amlodipine is a 1:1 blend of R and S enantiomers. Different studies on the racemic blend of (R) and (S) isomers, have demonstrated that the S (-) isomer of Amlodipine has a more prominent pharmacological impact. Various studies on amlodipine as a relocation of (3H) (-) PN 200-110 binding, demonstrated that displacement was stereo specific, with the S (-) isomer being 1000 times more potent than the R (+) isomer [7] i.e the S-enantiomer has 1000 times stronger affinity for the dihydropyridine receptor than the R-isomer [8]. The S-isomer has additionally got more extended half-life (49.6 hours) than the R-isomer (34.9) or the recemate (44.2 hours) [9]. Taking into account of these perceptions, it is trusted that the utilization of isolated S-amlodipine, the pharmacologically dynamic isomer of amlodipine, rather than the racemic blend, could be of colossal advantage as the required dosage and systemic side effects can be diminished [10].

The fourth generation L/N-type CCB, cilnidipine, a novel and unique dihydropyridine is approved for treatment of hypertension. Recent meta analysis demonstrates its good tolerability, safety and efficacy as an anti hypertensive, quite equivalent to amlodipine [11].

II. Aims And Objectives

Though Dihydropyridine calcium channel blockers are the first line of treatment of mild to moderate hypertension but appearance of ankle oedema is one of the limiting factors for their usage. So present study has been undertaken to compare the incidence of ankle oedema and its variation on the basis of gender, amongst commonly used Dihydropyridine Calcium Channel Blockers Amlodipine, s Amlodipine, Cilnidipine in mild to moderate hypertensive patients.

III. Materials And Methods

This is a comparative, non blinded, single centred, prospective and parallel groups, observational study was conducted in medicine OPD clinic of KIMS over a period of 9 months after obtaining approval from Institutional Ethics Committee and written informed consent from all patients who participated in the study in local language. As this is an observational study, we have only collected the data and the antihypertensive CCBs selection is done solely by treating physician. All newly diagnosed patients or patients on CCBs for less than one month, of either sex in the age group between 40 and 60 years with mild to moderate hypertension (mean diastolic BP between 90 and 110 mmHg) were enrolled for the study. Patients are selected on the basis of inclusion and exclusion criteria.

3.1 Inclusion Criteria

- Age : >40 yrs <60 yrs BMI >18.5 <30 kg/mtr²
- Sex : Both sex
- Patients with Essential hypertension of mild to moderate cases (stage I & stage II) according to JNC 7 (those with SBP < 180 and DBP < 110)

3.2 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, pregnancy induce hypertension.
- Patients of secondary hypertension or taking antihypertensive medicine ACEI / ARB or nitrates directly acting arteriolar dilator.
- Diabetes patients on pioglitazone.
- Serum creatinine >1.2 i.e renal disease
- Cerebrovascular disease
- Patient with liver disease,
- ACR > 30 mg/gm (Spot urine)
- Patients with heart failure, heart block, aortic stenosis
- On NSAID for long term or corticosteroid, sex or anabolic steroid.
- Any other chronic illness (RA, TB, PEM, filariasis)
- Alcoholic, Hypothyroid
- Vericose vein.

3.3 Baseline Parameters / Investigations

- Demographic parameters - (Age, sex, weight, height, BMI)
- Clinical parameters - Routine baseline values blood pressure, heart rate, clinical examination for any oedema or disease with volume overload.

- Biochemical parameters - Lipid profile (serum cholesterol , triglycerides , LDL , HDL , VLDL), Serum creatinine , urea, potassium , FBS & HBA1C , Spot urine albumin/ creatinine ratio, liver function test.
- TSH
- ECG & ECHO
- USG with Doppler whole abdomen.

3.4 Grouping Of Enrolled Patients

We have finally taken total 180 enrolled patients of mild to moderate hypertension attending KIMS medicine OPD and categorized them on the basis of gender first i.e male and female . Each category contains 90 patient, among which 30 patients are on Amlodipine (5 to 10 mg), 30 patients on s Amlodipine (2.5 to 5 mg) and 30 patients on Cilnidipine (10 to 20 mg). 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 of 14 days, one month, two months and three months for BP control and pedal oedema. Dose of Amlodipine, s Amlodipine and Cilnidipine are titrated according to their BP goal. We exclude the data of drop out participants, those who withdraw consent and those patients for whom additional anti hypertensive were added or any other protocol violation. Blood sugar, S. cholesterol, liver and renal function tests were repeated at 12 weeks to detect any drug induced bio chemical alterations.

The laboratory parameters assessed initially and at the end of the study like serum cholesterol, blood sugar, renal function tests , liver function test were also within normal limits. The subjective symptoms like flushing, palpitation and headache commonly associated with CCBs were not complained by the participants

3.5 Clinical Evaluation Of 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.

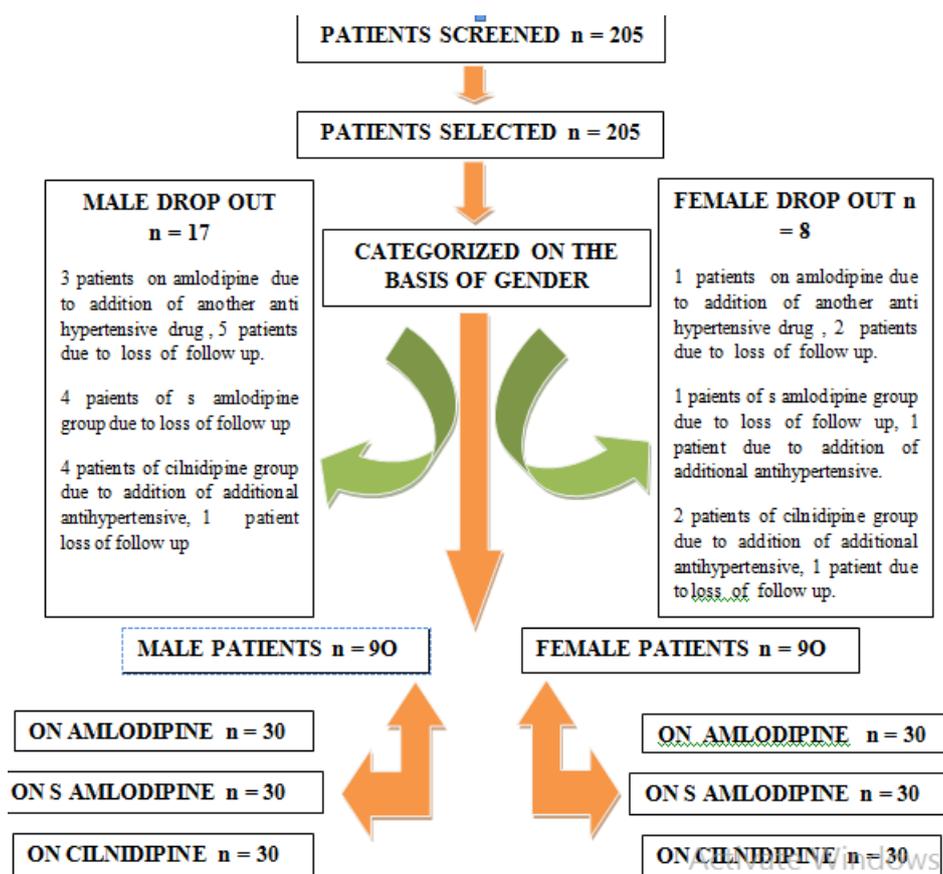
Ankle oedema is clinically evaluated by applying pressure over a bony prominence (proximal to lateral or medial malleoli).To provide effective compression finger pressure (right thumb) should be maintained for 20 to 30 second and evaluate pitting and time taking for rebound or disappear [32].

Pitting Oedema - measurement

1+	Barely detectable impression when finger is pressed into skin.
2+	Slight indentation. 15 seconds to rebound
3+	Deeper indentation. 30 seconds to rebound.
4+	> 30 seconds to rebound.

O’Sullivan, S.B. and Schmitz T.J. (Eds.). (2007). Physical rehabilitation: assessment and treatment (5th ed.). Philadelphia: F. A. Davis Company. p.659

205 patients were underwent screening and after selection they were divided on the basis of gender, of which 90 patients in each group completed the study. Following figure shows the participant enrolment and follow up.



On analysing the baseline characteristics of the patients, both the groups (male and female), and sub group (patients on Amlodipine, s-Amlodipine, Cilnidipine) were statistically similar in respect to age, BMI, SBP, DBP, (P<0.05) which is shown in Table 1,2 and 3.

RESULTS

Table 1: Comparison Of Demographic And Baseline Data Between Male And Female Groups			
Data analyzed	Male Patients	Female Patients	"Unpaired t test"* P Value**
Age* (Yrs) Mean ± SD Range	49.76 ± 6.1 40 - 60	50.41 ± 6.003 40 - 60	0.4722** (> 0.05)
BMI Mean ± SD Range	22.99 ± 3.21 18.57 - 29.11	23.55 ± 2.79 18.56 - 29.1	0.2133** (> 0.05)
SBP Mean ± SD Range	156.94±7.68 144 - 169	156.33±7.70 144 - 169	0.5953** (> 0.05)
DBP Mean ± SD Range	95.78 ± 6.341 80 -109	96.57±6.44 85 - 109	0.4080** (> 0.05)

Table 2: Comparison Of Demographic And Baseline Data Of The Male Patients (By One Way ANOVA)

Patients	Amlodipine n = 30	s- Amlodipine n = 30	Cilnidipine n = 30	Total n = 90	P* value
Age (yrs) Mean* ± SD Range	49.67** ± 6.29 42 - 60	49.37** ± 5.68 40 - 60	50.23** ± 6.48 40 - 60	49.76 ± 6.1 40 - 60	0.8581** (> 0.05)
BMI Mean* ± SD Range	22.50** ± 3.06 18.57 - 29.1	23.45** ± 3.65 18.77 - 29.11	23.01** ± 2.89 18.9 - 28.5	22.99 ± 3.21 18.57 - 29.11	0.5185** (> 0.05)
SBP Mean* ± SD Range	157.27**±7.66 144 - 169	156.73**±7.89 145 - 168	156.83**±7.74 145 - 169	156.94±7.68 144 - 169	0.9608** (> 0.05)
DBP Mean* ± SD Range	96.43**±6.31 84 - 109	95.03**±6.75 82 - 105	95.87**±6.08 80 - 106	95.78±6.341 80 - 109	0.6955** (> 0.05)

Table 3: Comparison Of Demographic And Baseline Data Of The Female Patients (By One Way ANOVA)

Patients	Amlodipine n = 30	s- Amlodipine n = 30	Cilnidipine n = 30	Total n = 90	P* value
Age (yrs) Mean*± SD Range	50.33**± 5.89 40 - 59	50.47** ± 6.41 40 - 60	50.43**± 5.91 40 - 60	50.41± 6.003 40 - 60	0.9961** (> 0.05)
BMI Mean*± SD Range	23.84**± 3.20 18.57 - 28.63	23.05**± 3.04 18.56 - 27.44	23.75**± 2.0 20.4 - 29.1	23.55 ± 2.79 18.56 - 29.1	0.4928** (> 0.05)
SBP Mean*± SD Range	156.37**±7.2 144 - 168	156.37**±7.21 146 - 169	156.27**±8.14 146 - 169	156.33±7.70 144 - 169	0.9984** (> 0.05)
DBP Mean*± SD Range	97.03**±6.47 85 - 109	97**±6.24 86 - 108	95.7**±6.73 85 - 109	96.57±6.44 85 - 109	0.6629** (> 0.05)

Table 4: Incidence Of Oedema Among Male Patients On Calcium Channel Blockers:

Data analyzed	Amlodipine	s Amlodipine	Cilnidipine	Total
Patients with Oedema* (%)	11** (36.7%)	2** (6.7%)	0** (0%)	13 (14.4%)
Patients Without Oedema (%)	19 (63.3%)	28 (93.3%)	30(100%)	77 (85.6%)

Total	30	30	30	90
By using the statistical method "Fisher's exact probability*" we get the exact p value** = 0.00009645, that is << 0.001. (statistically highly significant)				

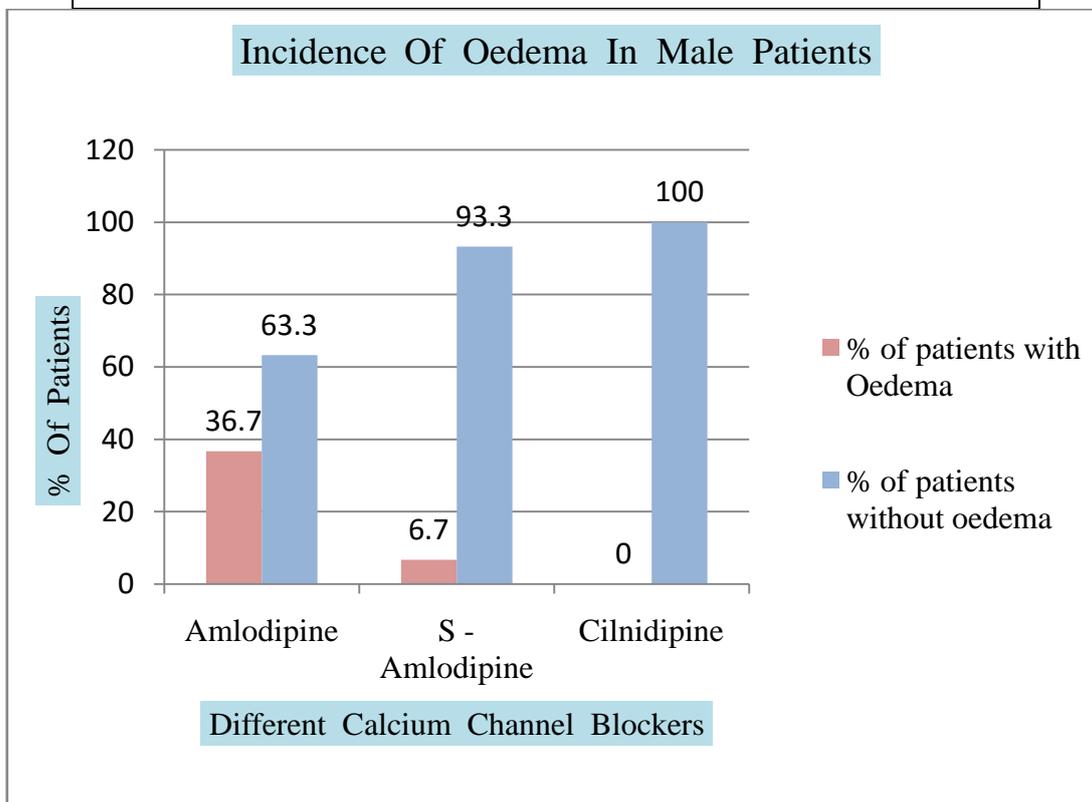


Table 5: Incidence Of Oedema Among Female Patients On Calcium Channel Blockers:

Data analyzed	Amlodipine	S Amlodipine	Cilnidipine	Total
Patients with Oedema* (%)	13** (43.3%)	3** (10%)	1** (3.3%)	17 (18.9%)
Patients Without Oedema (%)	17 (56.7%)	27 (90%)	29 (96.7%)	73 (81.1%)
Total	30	30	30	90

By using the statistical method "Fisher's exact probability*" we get the exact p value** = 0.00021077, that is << 0.001. (statistically highly significant).

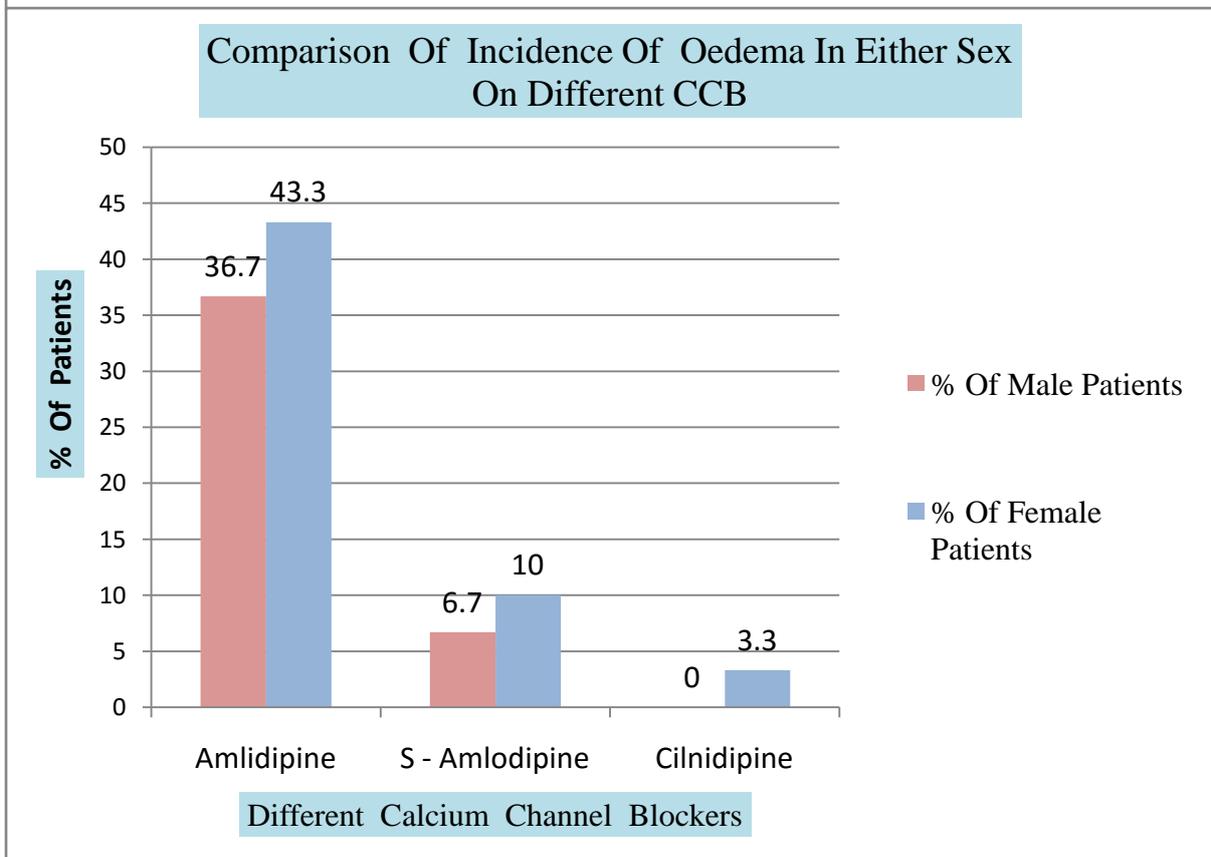
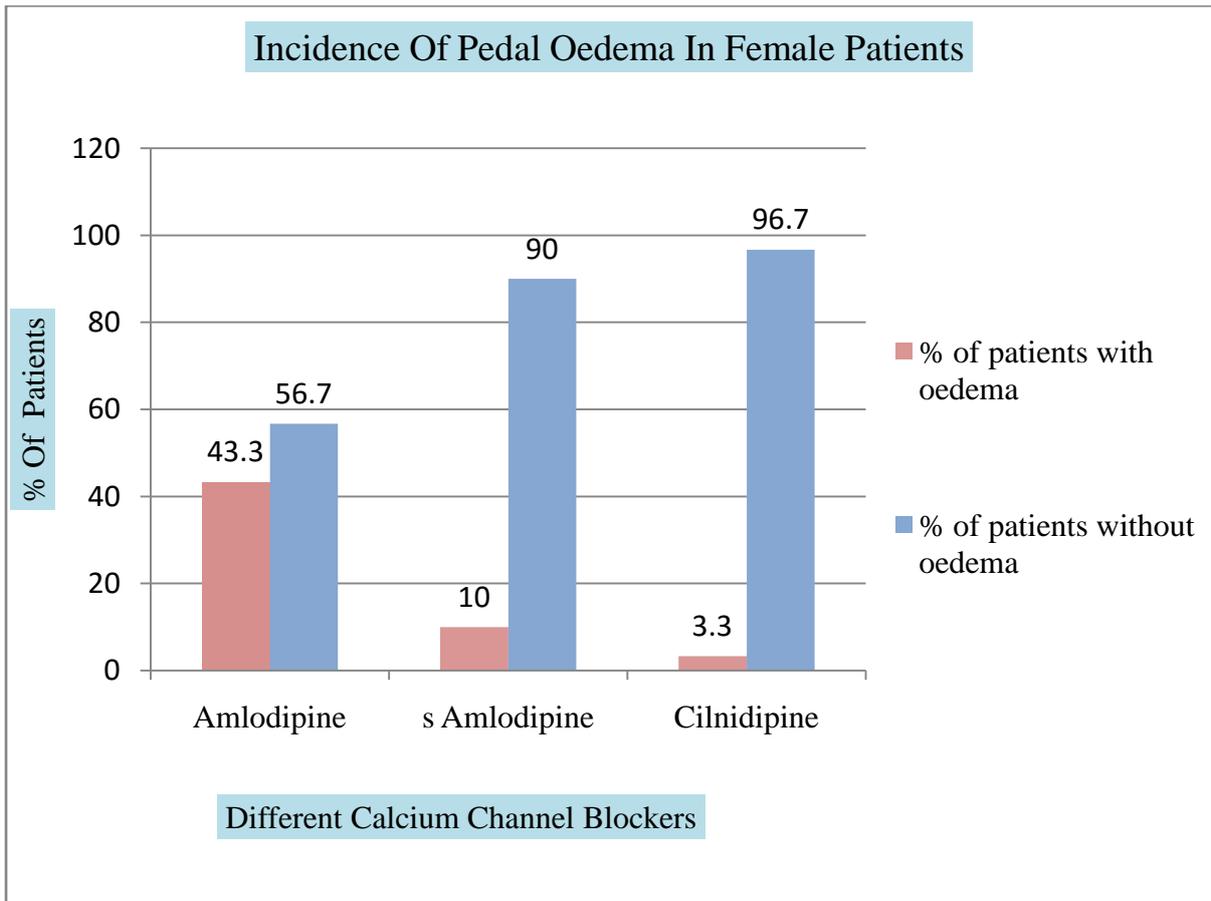


Table 6: Comparison Of Incidence Of Pedal Oedema

Between Male And Female On Different CCB			
Data analyzed	Male Patients with Oedema* (%)	Female Patients with Oedema* (%)	Fisher's exact probability* test P value**
Patients On Amlodipine n=30	11** (36.7%)	13** (43.3%)	0.79249424** (> 0.05)
Patients On s Amlodipine n=30	2** (6.7%)	3** (10%)	1.0** (> 0.05)
Patients On Cilnidipine n=30	0** (0%)	1** (3.3%)	1.0** (> 0.05.)

Table 7: Comparison Of Incidence Of Pedal Oedema Between S-Amlodipine And Cilnidipine In Male And Female			
Data analyzed	Patients On s-Amlodipine	Patients On Cilnidipine	Fisher's exact probability* test P value**
Male Patients with Oedema* (%)	2** (6.7%)	0** (0%)	0.4915** (> 0.05)
Female Patients With Oedema* (%)	3** (10%)	1** (3.3%)	0.6120** (> 0.05)

IV. Statistical Analysis

The differences in the incidence of pedal edema between amlodipine, s amlodipine and cilnidipine groups of either sex were compared by Fisher's exact test. For male group the exact p value is 0.0009645 and for female group the exact p value is 0.00021077, both of these p value is < 0.001 i.e. highly statistically significant. The incidence of oedema by calcium channel blockers can express simply as Amlodipine >>> s Amlodipine > Cilnidipine in both sex group. Cilnidipine cause lowest incidence of oedema.

The differences in the incidence of pedal edema between either sex were also compared for each drug i.e Amlodipine, s Amlodipine and Cilnidipine separately by Fisher's exact test. The exact p value for Amlodipine, s Amlodipine and Cilnidipine groups are 0.79249424 ; 0.1; 0.1 respectively, all are >0.05 i.e statistically not significant. Though the incidence rate of edema is more for females than that of males but of no statistical significance.

The difference in incidence of pedal edema between s Amlodipine and Cilnidipine in female patients were compared by Fisher exact test, p value is 0.6120 i.e >0.05,so it is not statistically significant. Same is also applicable for male patient group.Though the incidence rate of edema is apparently more by s Amlodipine than Cilnidipine but of no statistical significance.

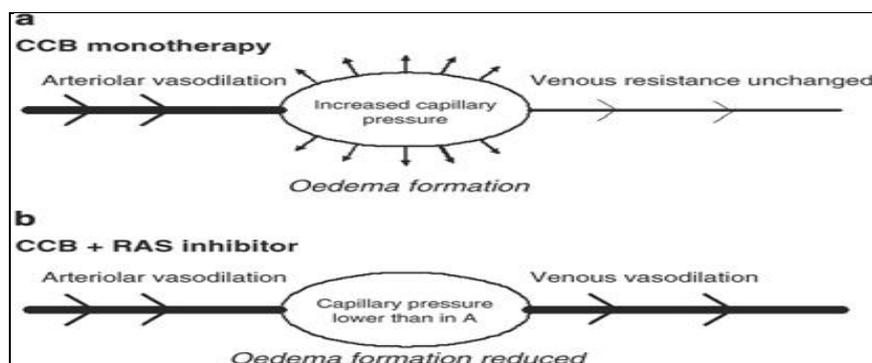
V. Discussion

The postulated mechanism for CCB induced ankle edema is as following:

1. The precapillary vasoconstriction in response to venous congestion, in normal individuals, protect the capillary bed from increased blood pressure.This further decreases the hydrostatic fluid filtration into the interstitium. L-type CCBs like amlodipine specifically inhibit pre-capillary constriction and causes arteriolar dilatations and hence causes interstitial edema [12].
2. Dilatation of pre capillary resistance vessels, and sparing of post capillary vascular tone by L-type CCB like amlodipine leads to capillary hypertension and interstitial fluid filtration [13].
3. CCBs causes extravasations of plasma protein and water into the interstitial space by increased microvascular permeability. [14,15].

CCB induced oedema can be decrease to some extent by ACE inhibitors or ARBs but not with diuretics, this proves that CCB induced oedema is not due to fluid retention [16,17,18,19]. Actually, a decrease in the ankle edema because of L-type calcium blockers is accounted for when these medications are combined

with ACEI, which have a vasodilatory impact on the venules. [20] This is additionally appropriate for ARB and nitrates.



(Effects of calcium channel blockers (CCBs), administered with and without a renin-angiotensin system (RAS) inhibitor, on capillary pressure and oedema formation (Figure redrawn from Figure 2 of Epstein et al. *Drugs* 2007;67:1309–1327). (a) CCB monotherapy; (b) CCB+RAS inhibitor. Dihydropyridine CCBs cause selective vasodilation 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.)

Cilnidipine is both N and L type calcium channel blocker. L-type calcium channel blockade causes pre capillary vasodilatation and arteriolar dilatation [21]. N-type Calcium channel blockade causes decrease sympathetic outflow by lowering plasma catecholamine that leads to further vasodilatation. As the sympathetic nerves also innervate the venules, the N type calcium channel blockers also cause venodilatation [22]. This twin activity result vasodilatation of both pre and post capillary resistance vessels and avert interstitial fluid hyperfiltration [23].

For this above mentioned reason, dual N and L type calcium channel blockers have a lesser incidence of ankle edema compared to only L type calcium channel blockers.

During our literature survey, it has been seen that only two clinical trials conducted on s Amlodipine. One study concluded that "s-Amlodipine 2.5 mg is equivalent in its efficacy and tolerability when compared to Amlodipine 5 mg in the treatment of mild to moderate hypertension" [24]. Another study concluded that "S-amlodipine 2.5/5.0 mg is found to be effective and well tolerated in the treatment of hypertension, and is an ideal switch over therapy for patients having peripheral oedema with conventional Amlodipine" [25]. Present study shows that s Amlodipine also cause ankle oedema though incidence is much lower than recemic Amlodipine. But apparently higher than Cilnidipine without any statistical significance. Same reports regarding ankle edema due to s-Amlodipine have been given by a study from Nepal [26].

The incidence of development of ankle oedema by CCB therapy is much more higher in women, older patients, those with heart failure, upright postures, and those in warm environments [27,28], this finding is additionally authenticating with present study. In present study it also seen that female are more prone to ankle oedema for all type of CCB. Other supportive publication, incidence rates of ankle edema "with DHP CCBs seen especially in women, and the edema is frequently dose related" [29,30]. One study conclude 272 out of 2000 (13.6%) patients was reported ankle edema with CCB monotherapy, "slightly but not significantly more common in women than men (15.6% vs. 11.8%)" [31]. The exact cause 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). The syndrome is poorly understood and almost occurs exclusively in females. It is generally unrelated to menstrual cycle, characterized by intermittent swelling of the face, trunk and limbs and by variation of weight. It is evident that increased capillary permeability in idiopathic oedema, leads to extravasation of fluid from the vascular compartment in the upright posture with secondary retention of sodium and water through the renin-angiotensin-aldosterone pathway activation [33, 34, 35]. There is no significant difference of cyclical edema found in the follicular and luteal phases of the menstrual cycle or in the pre- and post-menopausal patients [36]. Present study also shows female are more prone to ankle edema but there is no statistical significance.

VI. Conclusion

Amlodipine is associated with more incidence of ankle oedema in both sex group than s Amlodipine or Cilnidipine with highly statistical significance. Cilnidipine being N-type and L-type CCB, associated with much

lower incidence of pedal edema compared to only L-type channel blocker racemic Amlodipine. The less incidence of ankle edema by s-Amlodipine as showed in this study coincides with the fact that the R-enantiomer component could be the reason for the appearance of edema with racemic Amlodipine. Present study also shows female are more prone to ankle edema than male, but of no statistical significance. Though apparently s Amlodipine is associated with more incidence of oedema than Cilnidipine, but of no statistical significance.

VII. Limitations

The limitation of this study is, as it is a short duration study so further long term study is necessary in this regards, along with switch over therapy from Amlodipine to s Amlodipine or Cilnidipine in patients with ankle oedema. This could provide more appealing results regarding the side effect profile of s-Amlodipine with respect to ankle edema.

VIII. Footnotes

Conflict of interest: NIL

Source of support: NIL

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