INTRODUCTION

Extracellular Calcium ions perform a significant place in the physiology of muscle contractions. The entry of calcium ions lead to the contraction of smooth muscles and cardiac muscles resulting in constriction and contraction phenomena of blood vessels and heart respectively. If quantity of intracellular calcium ions decreases, force of myocardial contraction reduces which leads to vasodilation of coronary and peripheral arteries.\(^1\) The fundamental mechanism of inhibition of calcium influx has been utilized in managing conditions of high blood pressure and angina pectoris.

Drugs which inhibit calcium channels or calcium channel blockers are specific class developed with group of molecules with heterogenous chemical structures but with similar property of modulating association of calcium through voltage dependent channels present on cell membrane of smooth muscle cells and cardiac muscle cells.\(^2\)

Different chemical structures and pharmacodynamic heterogeneity of these calcium channel blockers are according to the position of the calcium channels which they inhibit. Some compounds are extra selective towards the channels present on the myocardium as compared to the vascular channels; classified as Phenylalkylamines. Dihydropyridines are more effective on the channels present on the blood vessels whereas Benzothiazepines work proportionately on both the heart and of the arterioles respectively.\(^1\) Dihydropyridines of Calcium-channel blockers, a distinct set constitutes compounds that are of significant difference in pharmacokinetics, and duration of action. Physiologically their property on target organs, BP, nervous system and heart rate also vary.\(^3\) Pharmacologically nifedipine and amlodipine are amongst the most evaluated calcium antagonists in the gastrointestinal therapeutic system as once daily formulation.\(^3\)
Amlodipine; available in global market since the year of 1992 has placed itself efficaciously in the list of antihypertensive drugs where both long term and short term trials has pointed out a position in effectively lowering mild to moderate blood pressure and relieves angina symptoms. Taking in to the consideration of comparative trials, its efficacy as antihypertensive is equal to that of other conventional antihypertensive molecules such as RAAS blockers, diuretics, beta receptor blockers, and other calcium mineral antagonists.\(^4\)

In a literature review by Levine et al; which included >5000 patients in the amlodipine monotherapy at the average daily dose of 5 mg showed reduction of 17.5 mmHg in systolic blood pressure from baseline where the effect was superior in elderly patients (age ≥60 years).\(^5\) A multicentric study in more than 5000 subjects with mild to moderate elevated blood pressure by Cross et al; showed that normalisation of blood pressure was obtained in over 80% of subjects with a mean reduction of 21/15 mmHg with the most common reported side-effect of edema.\(^6\) A Multinational population analysis from seven Asian countries conducted by Taylor et al; on more than 280 subjects showed that 63% subjects achieved their diastolic blood pressure target reduction with amlodipine 5mg once a day and 5 to 10 mg amlodipine once daily either as monotherapy or with other antihypertensive combination provided significant blood pressure lowering effect in general practice.\(^7\)

The blood concentrations of R- isomer and S- isomer were evaluated at after an administration of drug Amlodipine 20 mg racemic mixture, where S-enantiomer which is pharmacologically active was distributed more from the total amount of racemate. The mean values of Cmax of R-enantiomer were 47% and 53% for S-enantiomer. The active S-enantiomer even had lesser inter-subject variation as compared to its counterpart R-enantiomer (CV; R:52%, S:25%). The elimination from plasma was more rapid of R-enantiomer as compared to S-enantiomer. The terminal half lives of R-enantiomer was 34.9 h whereas to S-enantiomer was 49.6 h which directly narrates that the activity of S-enantiomer is responsible for long terminal half life of total Amlodipine (Mean 49.2 h). This difference is hypothesized mainly because of the differential blood clearance of enantiomer.\(^16\)
In a comparative clinical study the usefulness and safety of drug S-Amlodipine two point five mg against five mg racemate Amlodipine with Stage 1 and 2 Hypertension. 2.5 mg S-Amlodipine was administered in 97 patients whereas Amlodipine 5 mg treatment group had 91 patients. The analysis of study outcomes was performed by the help of Student’s’ test statistical test. The study objectives were decrease in blood pressure parameters including mean Diastolic and Systolic Blood force in different postures like standing, sitting and supine. The results showed significant difference in all the above mentioned parameters after six several weeks through management.

By way of S-Amlodipine 2.5 mg, reductions into BP were –

- Average SBP (standing) – Baseline: 164.12 mmHg, after treatment: 144.69 mmHg
- Average SBP (supine) – Baseline: 165.72 mmHg, after treatment: 146.04 mmHg
- Average SBP (sitting) – Baseline: 165.24 mmHg, after treatment: 145.36 mmHg
- Average DBP (standing) – Baseline: 99.63 mmHg, after treatment: 86.0 mmHg
- Average DBP (supine) – Baseline: 101.13 mmHg, after treatment: 87.18 mmHg
- Average DBP (sitting) – Baseline: 100.59 mmHg, after treatment: 86.27 mmHg

With Amlodipine 5 mg, the reductions in BP were –

- Average SBP (standing) – Baseline: 164.57 mmHg, after treatment: 154.42 mmHg
- Average SBP (supine) – Baseline: 166.47 mmHg, after treatment: 147.23 mmHg
- Average SBP (sitting) – Baseline: 165.81 mmHg, after treatment: 146.57 mmHg
- Average DBP (standing) – Baseline: 98.95 mmHg, after treatment: 86.19 mmHg
- Average DBP (supine) – Baseline: 100.86 mmHg, after treatment: 87.52 mmHg
Average DBP (sitting) - Baseline: 100.38 mmHg, after treatment: 87.33 mmHg

Notably, there were no significant difference with Amlodipine 5 mg drug and S-Amlodipine 2.5 mg drug for decrease of SBP and DBP in all the different kinds of postures (standing, supine, and sitting), p > 0.1. The secondary endpoints including SGPT, SGOT, serum creatinine, LDL, TG, HDL and total cholesterol levels did not show any significant change with Amlodipine 5 mg. But, S-Amlodipine 2.5 mg treatment group showed statistically non-significant reduction in total cholesterol and triglycerides. Concluding, for the treatment of hypertension S-Amlodipine 2.5 mg is equally efficacious and tolerable as compared to its racemate Amlodipine 5 mg.\textsuperscript{18}

A study on 18 healthy Korean males to evaluate S-Amlodipine formulation on the basis of pharmacokinetic and pharmacodynamic parameters. The results of this open label, random, double period, crossover, comparative study showed that S-Amlodipine was having comparable plasma concentration time profile as that of its racemate. The mean (SD) values for Cmax AUC for the S-Amlodipine did not differ significantly from Racemate Amlodipine. From baseline, significant difference was observed in maximal blood pressure and heart rate (p < 0.001). Concluding, Amlodipine racemate formulation was equivalent of pharmacodynamics and pharmacokinetics of S-amloidine.\textsuperscript{19}

Chiral switching – a method of utilizing pure racemate as a pharmaceutical active drug is becoming more and more popular theme in the development of drugs. In this study, baseline mean (SD) sitting SBP (SiSBP) was 142.6 mmHg and sitting DBP (SiDBP) was 96.9 mmHg in S(-)-amlodipine nicotinate group and it was 141.8 mmHg and 96.1 mm Hg in drug amlodipine group. The mean change in SiSBP (SD), were noted as 17.6 mmHg in S(-)-amlodipine nicotinate and 18.6 mmHg in drug amlodipine group. The responders rate for sitting DBP (SiDBP) were 92.7% and 88% for S-amlodipine group and amlodipine group respectively. The prevalence of Adverse Drug Reactions and Adverse Events were non-significant for both the treatment groups. Summarizing, there was non-inferior reduction in SiSBP observed at end of 8 weeks duration of
management with drug S-Amlodipine in comparison with its racemate i.e. Amlodipine. Even the rate of SiDBP was non-significantly different from the racemate with similar tolerability.\textsuperscript{20}

In a review article showed that S-amlodipine is vaso-active isomer of racemic mixture Amlodipine. In several clinical trials (Randomized controlled), it has confirmed that in the management of hypertension, half the dose of S-amlodipine is similar to the racemic Amlodipine. In the post marketing surveillance studies in more than 4000 patients, the occurrence of peripheral edema was negligible with S-Amlodipine as compared to Amlodipine (Racemic mixture) with preserved antihypertensive efficacy. Even in normotensive angina patients, S-Amlodipine at half the dose of racemate conferred antianginal efficacy. S-Amlodipine in fixed dose combinations with Atenolol and Hydrochlorothiazide was also effective and well tolerated. Considering all the above observations, S-Amlodipine as a monotherapy or in a dual therapy (combination) is an important alternative in the clinical managing of chronic disorders like Angina and Hypertension.\textsuperscript{21}

A comparative estimation of isomer S(-) amlodipine besylate and racemic Amlodipine was conducted on 63 subjects with hypertension, out of that 32 subjects were on racemic Amlodipine and 31 on S(-) amlodipine. The study objective was daily hypertension monitoring and office BP monitoring for antihypertensive effect which was obtained by both the formulations. The important finding was that S(-) amlodipine besylate daily dose was twice lesser than the racemic amlodipine daily dose. For the tolerability evaluation, lesser adverse effects (peripheral edema, headache) was observed in patients who received S(-) amlodipine besylate as compared to racemic (R+ S-) Amlodipine. Overall, a more positive and favorable clinical effects were observed with S(-) amlodipine besylate in the management of hypertensive patients.\textsuperscript{22}
An open label, non-comparative study was conducted for 10 weeks with an aim to assess the safety parameter of Amlodipine in mild to moderate hypertensive patients. Of the 5352 patients entering the study, 5135 received amlodipine; 4621 patients (90%) completed the study with a mean age of 58.2 years. In over 80% if patients, normalization of Blood pressure was achieved with a mean reduction of 21/15 mmHg. The mean final dose of amlodipine was 6.8 mg/day. Adverse experiences probably associated to amlodipine were reported by 19.3% subjects, and overall 6.7% of patients had withdrawal from the study due to adverse incidences. The frequent reported side-effect was edema. The frequency of headache was almost identical in older and younger patients and edema, flushing and dizziness were seen only slightly more often in elderly patients. 

A pooled database of clinical research studies, safety profile of Amlodipine. 4227 patients were enrolled in the study out of which 2495 patients received Amlodipine and the remaining patients received comparative agents (1213 on placebo, 519 on active comparators). Patients treated with Amlodipine had slightly higher prevalence or incidence of side effects as compared to placebo. The most common out of it was edema, which was usually well tolerated. This small database where different calcium channel blockers were compared, revealed that edema was common in Amlodipine treated patients whereas higher incidence of constipation were observed with Verapamil which is a non-dihydropyridine calcium channel blocker.

Vasodilators which are used in antihypertensive therapy are associated with blood vessel dilation swelling. This part outcome is associated with couple of mechanisms which includes –

- Dilatation of Arterioles (Arteriolar dilatation) which causes augment in intracapillary force

- Activation in Renin Aldosterone Angiotensin structure

- Retention of liquid volume
The side effect of vasodilatory edema is directly proportional to the drug dose. It is most common with the agents such as Minoxidil or Hydralazine which are direct arteriolar dilators. This effect decreases in descending order as dihydropyridine calcium channel blockers, beta blockers, antiadrenergic agents and nondihydropyridine calcium channel blockers. From this study, it was observed that the frequency of vasodilatory edema is not the same in all dihydropyridine calcium channel blockers. With equal effect on hypertension control, Amlodipine and Nifedipine had higher incidence of edema as compared to Lercanidipine or Lacidipine. Vasodilatory edema is significantly reduced with the addition of agents acting on enzyme angiotensin adrenal gland hormone arrangement such as plasma protein converting enzyme blockers (ACEIs) or plasma protein receptor blockers (ARBs) to the calcium channel blockers.\textsuperscript{10}

The occurrence of leg edema with calcium channel blockers. The mechanism of edema is related with blunted postural skin vasoconstriction which is a phenomena that is autoregulated and it minimizes the increase in capillary pressure due to gravitational force and thus avoids fluid extravasation in standing posture. For the evaluation of dose response relationship between the pharmacological mechanism mentioned and frequently observed side effect of edema with calcium channel blockers, skin blood flow with the help of laser flowmetry of foot in both inclined and with legs 50 cm lower the heart level and leg weight through Archimedes principle were measured. These measurements were done at baseline, followed by increasing doses of dihydropyridine calcium channel blocker (for 2 weeks, 5 and 10 mg UIB each), as well as after withdrawal of drug in 10 men suffering from hypertension. Leg weight was increased with Amlodipine 5 mg UID. This effect was observed without any modification of postural vasoconstriction which indicates that extravascular fluid shift is not related to vasoconstriction. But at 10 mg Amlodipine UID, the postural vasoconstriction was blunted and leg weight was increased suggesting that autoregulation of skin blood flow limits the transfer of additional fluid.\textsuperscript{24}
The dose dependent adverse effect which is a limitation of antihypertensive therapies. Pedal edema is a dose limiting side effect of a potent dihydropyridine calcium channel blocker that is Amlodipine Besylate. The study by Malaco E and his team compared the valsartan and amlodipine therapies in elderly patients with isolated systolic hypertension (abbreviated as ISH) on the basis of risk/benefit profile. In the results obtained, 31.9% patients treated with Amlodipine had adverse effects as that of 20.2% patients on Valsartan (p < 0.003). The rates of peripheral edema were 26.8% with amlodipine whereas 4.8% with valsartan (p < 0.001). In these elderly patients with ISH, the treatment with valsartan as monotherapy or in combination with 12.5 mg Hydrochlotothiazide showed similar efficacy with better tolerability as compared to Amlodipine based treatment regimen.25

The edema formation by two calcium channel blockers was compared. This was done by quantitative assessment of foot volume by an accurate method. In this randomized study, 62 patients suffering from essential hypertension were treated either with drug lacidipine 4 mg once daily (N = 30) or with drug Amlodipine 5 mg once daily (N = 32) for 12 week duration. At the end of 6 weeks, response of diastolic blood force response was found insufficient i.e. more than 90 mmHg and decrease less than 10 mmHg. Most frequent observation was edema which was scored visually (p=0.02) with drug Amlodipine (15/32) compared with drug Lacidipine (6/30) that was verified by augment in foot volume > 95% by higher limit of normal variation. Non-significant difference in Lacipidine and Amlodipine groups were observed in both the parameters i.e. increase in foot volume and reduction in blood pressure. Concluding, the higher prevalence of swelling were observed with Amlodipine treatment as compared to Lacidipine treatment possibly because of comparatively higher c.q. and a greater antihypertensive effect of Amlodipine.26
A case report of nonfatal intentional overdose of Amlodipine was studied. In this case, a woman; age 42 years suffering from hypertension ingested 50-100 mg of Amlodipine with at least 40 ounces of beer for suicide attempt. The following were the mild symptoms observed -

- BP range - 79/50 to 113/76 mmHg.
- Heart rate range - 92 to 129 beats per minute showing sinus tachycardia.

This case of Amlodipine overdose showed sustained reduction in blood pressure (hypotension) and sinus tachycardia with transient pulmonary edema following fluid replacement (Low volume). The overdose of Amlodipine produces hemodynamic effects which are prolonged and may lead to pulmonary edema. Because of the long elimination half-life and delayed onset of effects, an aggressive decontamination therapy should be provided to patients who have overdose of amlodipine. Even these patients if are hemodynamically unstable may require supportive care with extended clinical monitoring.

The major attributes for Amlodipine including chemistry, pharmacology, pharmacokinetics, pharmacodynamics and adverse effects. Amlodipine has high selectivity towards vascular smooth muscle cells with minimum effects on cardiac parameters i.e. myocardial contractility or heart conduction. This property confers potent peripheral and coronary vasodilation of Amlodipine. Pharmacokinetic parameter showed slow absorption after oral administration, with half-life ranging from 36 - 45 hours. United States Food and Drug Administration has approved Amlodipine for the treatment of coronary artery disease and hypertension. Even this drug is used in hypertensive and anginal subjects with congestive cardiac collapse due to upper blood pressure malfunction classified as II and III by New York Heart Association. 24 time management of high blood pressure and Angina is acquired with once a day management of Amlodipine in the amount variety of 5-10 mg either as only one medication treatment or in a two medication mixture with other drugs. No significant drug interactions with Amlodipine were observed. No unfavorable or adverse effects on serum glucose or lipid levels have been observed.
with Amlodipine. Peripheral edema was the most common adverse effect with Amlodipine. These findings are endorsed by several clinical studies. Summarizing, Amlodipine as a monotherapy or in combination is efficacious and fine accepted in therapy of High blood pressure and Angina.  

The experience of pedal edema were compared on female Korean subjects with mild to moderate hypertension who were treated either with drug S(-)-amlodipine or drug amlodipine. These subjects were randomly assigned on drug S(-)-amlodipine daily or drug amlodipine once a day for duration of 12 weeks in this multicenter, actively controlled, double blind, Phase 4 clinical study. The primary objective of the study was Ankle foot volume measurement. The changes in mean diastolic and systolic blood pressure were secondary parameters of the study. The results showed that hypertensive patients on S(-)-amlodipine nicotinate had lesser incidences of ankle edema as compared to amlodipine besylate with similar blood pressure lowering efficacy. Thus concluding, in patients intolerant to drug amlodipine, drug S(-)-amlodipine can be a convenient option.  

Illustration of the problem for reporting frequency of edema and severity with accuracy.

- **Mild** - On examination edema is present; patient was not aware (asymptomatic) and it did not affected the daily living. Patient was ready to continue the medication used in the study.

- **Moderate** - On examination edema is present. Subject was ready to persist the prescription used in the study.
• Severe - On examination edema is present; patient was aware (symptomatic) and it affected the daily living. Subject was not ready to continue the medication used in the study.

In this study, this above mentioned category assessment were highly subjective although the same objective criteria were utilized for assessing the peripheral edema.\textsuperscript{31}

The modes of frequency mentioned as mild, moderate and severe for the determining the presence of edema were incomplete as the frequency or occurrence of peripheral edema before the initiation of treatment of calcium channel blocker was rarely identified. In general population, the occurrence of transient edema was quite common which were related to the posture, climatic conditions and age.\textsuperscript{32}

The occurrence of calcium antagonist - related edema can also be related with already / pre-existing edema, where cumulatively the frequency becomes severe. This analysis was performed where it was evaluated that the causative factor for CCB-related edema was preferential arteriolar or precapillary dilation which was not equal to the dilation in the venous or postcapillary circulation.\textsuperscript{33}

**SCOPE OF RESEARCH**

A study for identifying a practical approach for the evaluation of drug induced adverse effect of pedal edema. Increased pedal edema which was detected by segmental bioimpedance was compared with methods such as scientific pitting measurement, perimeter of ankle and water dislocation volumetry. The learning inhabitants consisted both, the healthy subjects and hypertensive patients. The results showed that fragmental were equivalent with methods like stream disarticulation and perimeter. But it carried out or was superior than the clinical consideration of pitting for ankle edema. This study results support the detection method to measure pedal edema stimulate by Amlodipine.
Amlodipine, one of the most commonly used antihypertensive agent with wide array of clinical evidence however is associated with adverse events such as peripheral edema, flushing, and headache which are frequently the reason for patient non-adherence and non-compliance to the treatment.

A study comparing amlodipine and its racemate S-amlodipine should be performed to evaluate its side effects profile along with effectiveness.

**PROBLEM ON HAND**

Calcium Channel Blocker related peripheral edema can reduce patient adherence and in clinical practice, it is often the most common reason for the clinician to discontinue the prescription of these drugs. This side effect is correlated to numerous mechanisms, including activation of the renin-angiotensin-aldosterone program, arteriolar dilatation, and liquid quantity retention.

Basically, it is due to a reduction in arteriolar resistance which is disproportionate to that of the venous circulation which augments circulation pressures of precapillary region and allows fluid transfer into interstitial space. Calcium antagonists related edema is based on gender discrimination where it is general in females and relate to supine position, age, and preference of the calcium channel blockers. Patients complaining of peripheral edema must be evaluated for etiology related to drug and nondrug. Instead of reducing dose of calcium channel blockers or shifting to another molecule single drug or two drugs combination (e.g, CCB plus RAAS inhibitor) can improve efficacy of hypertension control, normally with lower strengths of individual drugs reduces adverse events risk.

A Prescription-Event Monitoring Study by Kubota et al; conducted during 1984 and 1991 on 37,670 patients treated with different CCB’s showed that the non-dihydropyridines like diltiazem leads to lower incidence of vasorelaxation related events compared with vasoselective
dihydropyridines (amlodipine and nifedipine). Notably, 2 to 4 times higher rate of edema than flushing, dizziness or headache. Papavassiliou et al. in 2001 showed that as compared to other calcium channel blockers, significantly higher percentage of incidences of peripheral edema are associated with Amlodipine treatment (22%). Leonetti et al; from the COHORT Study1 on around 800 geriatric patients, provided a conclusive data regarding the most frequent side effect of dihydropyridine calcium channel blockers include pedal edema. It showed that Amlodipine had a greater incidence of pedal edema (19 %) compared to lacidipine (4 %) and lercanidipine (9 %).

RESEARCH OBJECTIVE

Structurally, Amlodipine is a chiral calcium antagonist which remains blend combination with R enantiomer plus S enantiomer within similar relative amount. Levoamlodipine also known as Levamlodipine or levoamlodipine is a pharmacologically active monomer of amlodipine. Studies which aimed at receptor binding and configuration analysis evaluated that out of the two isomers only S-enantiomer and not the R-enantiomer binds and blocks L-type of voltage gated calcium channels. This calcium antagonistic action that is only resides with S-amlodipine. Hence, S-amlodipine is 1000-folds more active than R-amlodipine. Studies in rats with condition of spontaneous high blood pressure suggests that R-isomer dihydropyridine does not decrease the plasma force at all at the same time as S-amlodipine lowers the blood pressure efficiently. The R-stereoisomer that is dormant as a mineral antagonist thus comprises an adulteration and grounds an augmented drug related weight on the body as soon as mixture dihydropyridine is worn in medical perform. Plasma elimination of R-amlodipine is more faster than S-amlodipine. R-amlodipine has average terminal half-life of 34.9 hrs and S-amlodipine has 49.6 hours. Thus S – enantiomer confers longer duration of action to Amlodipine. And selective usage of S-amlodipine alone will confer extra longer duration of action than the mixture. S-amlodipine augments pharmacokinetic advantages of Amlodipine. A systemic plasma clearance of isomers may play a crucial role in observation of enantioselectivity of amlodipine. Use of isolated S-
Amlodipine, the pharmacologically active isomer of amlodipine instead of the racemic mixture could be of immense benefit as the required dose and systemic toxicity can be reduced.

Hence, the current study has been conducted to assess the efficacy and tolerability of drug S-amlodipine with that of racemic mixture of drug amlodipine in patients with hypertension. The prime intention was to evaluate the effectiveness of S-Amlodipine half dose single in a daily with drug Amlodipine full dose single in a day for treatment of hypertension upon switching patients from Amlodipine to S-Amlodipine and Secondary objective was to assess the tolerability of drug S-amlodipine by switching patients from Amlodipine