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A Randomized, Prospective Study to Compare the Efficacy and Tolerability of S-Amlodipine 2.5mg versus Racemic Amlodipine 5mg in Mild to Moderate Hypertension.

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Research Article

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ABSTRACT

To compare the efficacy and tolerability of S-Amlodipine 2.5mg with racemic amlodipine 5mg in mild to moderate hypertension. 108 newly diagnosed patients with mild to moderate hypertension were enrolled. After randomization, 54 patients were assigned to receive S-Amlodipine 2.5mg and 54 patients to receive racemic amlodipine 5mg once daily for 12 weeks. Blood pressure, heart rate, ankle circumference and other adverse reactions were monitored every 2 weeks. Fifty patients in each group completed the study. The results were analyzed by Students t' test. At 2&6 weeks, R amlodipine group showed a better efficacy in reducing both systolic and diastolic B.P ($p=0.0001$). At 12 weeks, both the study groups showed an equivalent efficacy in reducing the mean systolic (32.410.8; 29.6±9.0) and diastolic (13.45.9; 12.0±9.9) blood pressures ($p=0.16$ & 0.38). There was a significant increase in the mean ankle circumference in the Racemic amlodipine group compared to S-amlodipine group at 2, 6 & 12 weeks ($p<0.05$). There was no statistically significant change in renal & liver function tests. S-amlodipine 2.5 mg is found to be equivalent in efficacy and better in tolerability compared to Racemic amlodipine in mild to moderate hypertension at 12weeks.Racemic amlodipine proves to be more potent than s-amlodipine in reducing blood pressure.

INTRODUCTION

Systemic hypertension is one of the most common maladies of mankind affecting about 20% of population globally [1]. All sections of population in India suffer from the disease, with higher prevalence in urban (30.9%) than the rural population (21.2%). Most of the patients with early hypertension have no symptoms but a regular monitoring of blood pressure attributes to early detection of hypertension [2]. As per 2007 AHA guidelines, Calcium channel blockers are one of the first line drugs in uncomplicated hypertension [3]. SYST-EUR trial reveals a decrease in cardiovascular mortality and morbidity in patients of isolated systolic hypertension with the long acting calcium channel blocker amlodipine [4].

Amlodipine, the III generation dihydropyridine differs from other DHPs in its pharmacokinetic properties such as slow absorption and long $t_{1/2}$ (40hrs). It produces both peripheral arterial and coronary vasodilatation and less reflex tachycardia. It can be administered as a convenient single dose starting from 2.5mg which can be increased up to 10mg [5]. Though amlodipine is advantageous as antihypertensive in many grounds, the side effect of ankle edema necessitates discontinuation in 9.3% of patients [6]. This non-compliance may contribute significantly to poor BP control and hypertension-related morbidity and mortality. The addition of a second agent increases the risk of non-adherence by increasing the pill count and possibly exposing the patients to a second set of adverse effects.

Structurally, Amlodipine is a racemic mixture of two enantiomers, S and R. Since amlodipine racemic mixture has more preferential action over arteriolar smooth muscle than the veins, capillaries in feet are exposed to un-physiologically high hydrostatic pressure owing to pre-capillary dilatation and reflex post capillary constriction

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which causes exudation of fluid by Starling mechanism [7]. This edema is not relieved by diuretics, but can be reduced to some extent with ACE inhibitors and ARBs, which proves the fact that edema with amlodipine is not the result of fluid retention [8,9,10,11].

Chiral switching or unichiral version of the racemic drug has been proposed to be a means of obtaining safer alternatives to existing racemates. In Racemic amlodipine R isomer is inactive as CCB and is thought to be responsible for pedal oedema . S-Amlodipine, the newer compound contains only the S- enantiomer of Amlodipine. A longer half-life (49.6 hours) than the R-isomer (34.9hrs) or the recemate (44.2 hours), consistent pharmacokinetics compared to R-isomer, efficacy at half the racemate dose, less metabolic load , prevention of accumulation of R-isomer in elderly and negligible pedal edema are the added advantages of the S-isomer [8].

Previous Studies have revealed that incidence of edema was much lower with S-Amlodipine (1.3%) and interestingly blood pressure was reduced at half the dose of racemic amlodipine [8]. Since fewer studies are available in our country in this regard, we aimed to evaluate the concept of chirality by comparing the efficacy and tolerability of Racemic amlodipine 5mg O.D to S-amlodipine O.D at the half its racemate dose (2.5mg) in patients with mild to moderate hypertension.

MATERIALS AND METHODS

This Randomized, comparative, single blinded, single centred, prospective and parallel group study was conducted in Hypertension clinic of a tertiary care hospital over a period of 12 months after obtaining approval from Institutional Ethics Committee and written informed consent from all patients who participated in the study in local vernacular language.

All newly diagnosed patients of either sex in the age group between45 and 75 years with mild to moderate hypertension (mean diastolic BP between 90 and 110 mmHg) were enrolled for the study.

Patients with diastolic BP >110mmHg, cardiovascular and cerebrovascular disorders were excluded from the study. Pregnancy induced hypertension and patients found to have secondary hypertension were not considered for the study. Diabetics and patients already on anti-hypertensive drugs were not included for the study. After assessing nutritional status, peripheral edema, jaundice, cardio respiratory status, abdomen and fundus examination, patients were subjected to baseline laboratory investigations such as urine analysis, blood glucose, urea, serum cholesterol, creatinine, liver function tests , X ray-chest, ECG and ultra-sonogram abdomen.

After randomization by using computerised random number table, 54 patients assigned to the control group were given Amlodipine 5mg and 54 patients to the test group were given S- Amlodipine 2.5mg once daily in the morning for 12 weeks along with advice for salt restriction (no added salt) and regular physical activity. Adequate blinding was done by giving similar tablet to the patients of both the groups. Patients were instructed to attend the hypertension clinic fortnightly to receive drugs for 14 days and to report immediately in case of any adverse event. Adherence was monitored by pill count. Clinical response was assessed in both control and test groups every 2 weeks. It was planned to withdraw patients from the study if they do not attain a SBP reduction of ≥10mmHg from the baseline at 6weeks [12].

Patients in both the groups were followed up every 2weeks for BP measurement (sitting SBP/DBP) by using standard mercury sphygmomanometer after 10 minutes of rest and ankle circumference measurement 5 cm above midpoint of medial malleolus to look for edema. Blood sugar, S. cholesterol, liver and renal function tests were repeated at 12 weeks to detect any drug induced bio chemical alterations.

The baseline characteristics of both the study groups were matched by unpaired Student 't' test and Pearson's chi-square test. The efficacy and tolerability of the drugs within the group was analyzed and interpreted by paired 't' test and between the study groups by unpaired 't' test in different intervals. Independent student 't' test was used to analyze the laboratory parameters. The above statistical analysis was done in S.P.S.S. (Statistical Package for the Social Sciences) (version-13.0). The p values of less than 0.05($p<0.05$) were considered statistically significant.

RESULTS

Of the 328 patients who underwent screening, 108 were randomly assigned to study groups , of which 50 patients in each group completed the study. [Figure 1] shows the participant enrolment and follow up.

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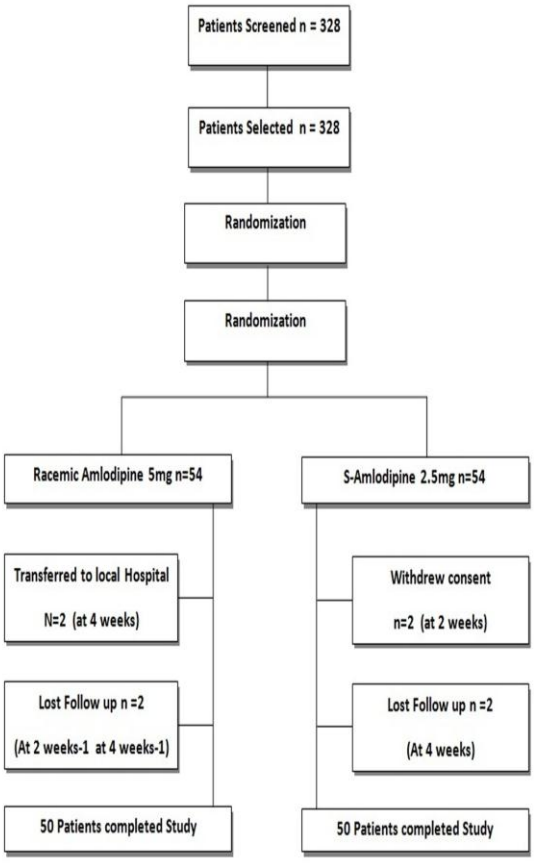
Figure 1



On analysing the baseline characteristics of the patients, both the groups were statistically similar in respect to age, sex, SBP, DBP, ankle circumference, liver function tests and renal function tests (P<0.05) which is shown in Table 1.

TABLE 1

BASE LINE PARAMETERS-mean	RACEMIC AMLODIPINE(N=50)	S-AMLODIPINE(N=50)	P VALUE
Age	55.5	57	0.476
Sex	24 males,26 females	22 males.28 females	0.68
Systolic blood pressure	154.4mmHg	152.2mmHg	0.312
Diastolic blood pressure	98.6mmHg	97.2mmHg	0.194
Ankle circumference	20.11cm	20.13cm	0.954
S. cholesterol	145.52	161	0.1077
Blood sugar	109.08	116.22	0.2718
Liver function tests			
Serum bilirubin	0.75	0.778	0.4485
Serum protein	6.548	6.49	0.6637
Serum albumin	4.012	3.906	0.2972
SGOT	30.04	29.48	0.6988
SGPT	30.48	31.32	0.5748
Renal function tests			
Blood urea	25.94	28.54	0.0834
S. Creatinine	1	0.954	0.2936

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Eficacy analysis of racemic amlodipine and S-amlodipine was done at 2,6 and 12weeks. At 2weeks, Racemic amlodipine reduced mean systolic blood pressure to 133mmHg from the mean baseline value of 154.4 mmHg, whereas S-amlodipine reduced mean systolic B.P to 140.8mmHg from the mean baseline value of 152.2 mmHg. In both the cases reduction was significant(p =0.0001,0.0001).

On analysing the data at 6th week, it was found that the group assigned to racemic amlodipine recorded a decreased mean SBP of 125.4mmHg compared to the baseline value of 154.4mmHg and the group with S-amlodipine had a fall to 132mmHg from the baseline mean SBP of 152.2mmHg. This reduction in both the groups was found to be significant (p=0.0001,0.0001).

At 2weeks, mean diastolic blood pressure was reduced from the baseline value of 98.6mmHg to 88.2mmHg by racemic amlodipine whereas S-amlodipine reduced mean diastolic B.P to 90mmHg from the baseline of 97.2mmHg. (p=0.0001, 0.0001). Mean DBP of patients treated with racemic amlodipine was 85.8mmHg and with S-amlodipine 88mmHg at 6weeks(p=0.0001.0.0001) [Table 2]

TABLE 2

Variable	Duration	Racemic Amlodipine (n=50)			S- Amlodipine (n=50)		
		Mean	SD	p	Mean	SD	P value
SBP(mmHg)	Baseline	154.4	11.8	--	152.2	9.7	--
	2wks	133	10.3	0.0001	140.8	13.1	0.0001*
	6wks	125.4	9.7	0.0001	132	9.7	0.0001*
	12wks	122	9.7	0.0001	122.6	6.6	0.0001*
DBP(mmHg)	Baseline	98.6	3.5	--	97.2	6.1	--
	2wks	88.2	5.2	0.0001	90	5.7	0.0001*
	6wks	85.8	5.4	0.0001	88	4.5	0.0001*
	12wks	85.2	5	0.0001	85.2	5.8	0.0001*
Ankle Circumference (cm)	Baseline	20.01	1.9	--	20.13	1.8	--
	2wks	20.11	1.9	0.01	20.13	1.8	--
	6wks	20.24	2	0.008	20.13	1.8	--
	12wks	20.27	2	0.0055	20.15	1.8	0.1593

* P Value statistically highly significant

On comparing the difference between the reduction of systolic Blood Pressure by both study drugs, more significant reduction was observed in mean SBP of patients treated with racemic amlodipine compared to S-amlodipine at both 2&6 weeks(p=0.0001 ,0.0001).

Also the reduction of mean DBP is more with racemic amlodipine compared to S-amlodipine at both 2& 6weeks(p=0.0245,0.013).

At 12 weeks of therapy, the mean reduction of systolic blood pressure in racemic amlodipine group from baseline was 32.4±10.8mmHg(p=0.0001). In S-amlodipine group, mean reduction of systolic blood pressure from baseline to 12th week was 29.6±9.0mmHg (p=0.0001).

Amlodipine produced a mean reduction of 13.4±5.9 mmHg in diastolic blood pressure from the baseline which was stastically significant(p=0.0001). In group of patients treated with S amlodipine ,the mean reduction of diastolic blood pressure from baseline was 12.0±9.7mmHg(p=0.0001)

At 12weeks of therapy, efficacy was compared between racemic amlodipine and S-amlodipine. The mean reduction in systolic blood pressure was 32.4±10. 8 mmHg in racemic amlodipine group compared to 29.6±9.0 mmHg in S-amlodipine group. The mean difference between the study groups was statistically not significant (p=0.1626). The group treated with racemic amlodipine showed a mean reduction in diastolic blood pressure of 13.4±5.9mmHg compared to 12.0±9.9 mmHg in S-amlodipine group. There was no significant difference between the two drugs (p=0.3853). [Table 3]

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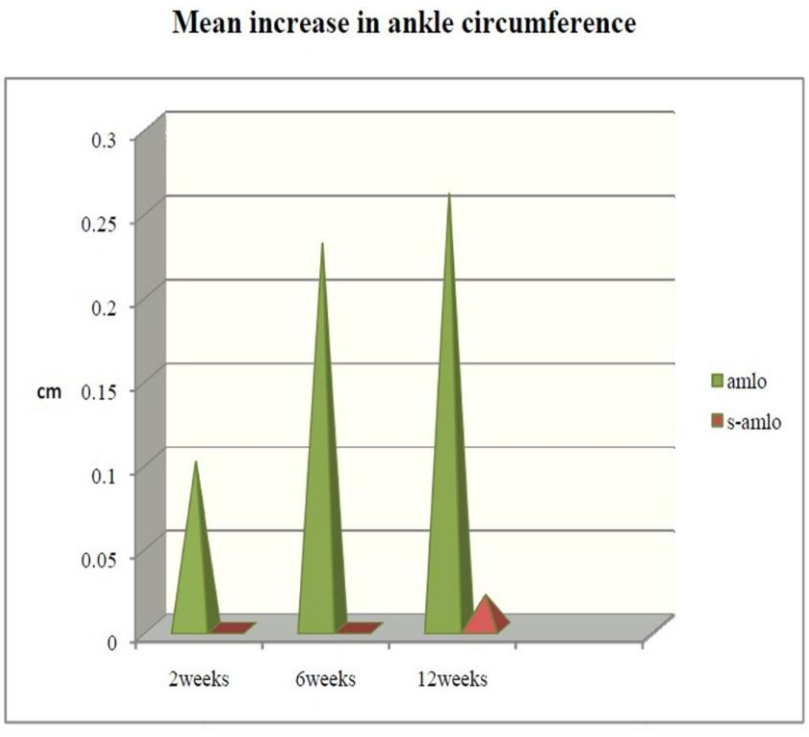
TABLE : 3

Variables & Duration		Amlodipine (n=50)		S Amlodpine (n=50)		
		Mean Reduction From baseline	SD	Mean Reduction From baseline	SD	P value
SBP(mmHg)	2wks	21.4	9.3	11.4	9.9	0.0001
	6wks	29	11.3	20.2	8.2	0.0001
	12wks	32.4	10.8	29.6	9	0.1626*
DBP(mmHg)	2wks	10.4	5.7	7.2	8.1	0.0245
	6wks	12.8	5.7	9.2	8.3	0.013
	12wks	13.4	5.9	12	9.9	0.3853*
Ankle Circumference (cm)	2wks	0.11	0.27	0	0	0.0095
	6wks	0.23	0.59	0	0	0.007
	12wks	0.26	0.63	0.02	0.09	0.009

*P value >0.05 (not significant)

Regarding the appearance of ankle edema which is assessed by the mean ankle circumference in both the study groups, racemic Amlodipine produced a significant increase in mean ankle circumference at 2, 6 &12 weeks from the baseline value of 20.01cm(p=0.010, 0.008,0.0055). S-amlodipine produced no significant increase in ankle circumference during the study period (p=0.1593), shown in figure 2.

Figure 2



The comparison of mean ankle circumference between both the study groups, showed a significant increase with racemic amlodipine compared to S-amlodipine in 2,6 and12 weeks (p=0.0095,0.007,0.0094). [Table3].

The results of laboratory tests done at baseline and 12weeks of the study, revealed no significant changes in both the groups. No other specific adverse reactions were observed during the study.

DISCUSSION

As per literature, both systolic and diastolic blood pressures increase with age till 55years after which the diastolic pressure decreases and the systolic pressure progressively increases resulting in isolated systolic hypertension [13]. The prevalence of hypertension among men and women in this age group are 43.6% and 53.7% respectively according to National Health and Nutrition Examination Survey(1999-2000). This study included patients with mean age of 55.5 years in racemic amlodipine group and 57 years in S-amlodipine group with no statistical difference between both the study groups. This study included 52% females, 48% males in racemic group and 56% females, 44% males in the S-Amlodipine group showing a slight preponderance to females which correlates with global prevalence in this age group [14].

The mean baseline blood pressure of patients randomly allocated to racemic amlodipine and S-amlodipine group was 154.4 mmHg, 152.2 mmHg (systolic) and 98.6 mmHg, 97.2 mmHg (diastolic) respectively which falls in the category of Stage I and II hypertension in JNC 7 classification [13,15]. There was no statistically significant difference in mean baseline blood pressure between the study groups.

The baseline results of the laboratory investigations such as serum cholesterol, blood sugar, liver and renal function tests done for the study patients were compared between the two groups and found to be insignificant. Physical examination done at every fortnight and the laboratory parameters excluded the cardiac, hepatic and renal causes for peripheral edema.

This study observed that the mean SBP and DBP were significantly reduced from baseline in both the study groups at 2,6 and 12weeks($p<0.0001$) proving the efficacy of both the study drugs in reduction of blood pressure to target level. By comparing the results between the groups, the mean reduction in SBP and DBP at 2&6 weeks were significantly more in racemic amlodipine group compared to S-amlodipine (SBP: $p<0.0001$ at 2&6 weeks and DBP: $p=0.0245$at 2wks, $p=0.013$ at 6weeks), whereas at 12 weeks the mean reduction in SBP(32.4±10.8 and 29.6±9.0 mmHg) and DBP (13.4±5.9 and 12.0±9.9mmHg) by both the study groups were almost similar ($p=0.16$and $p=0.38$ respectively). This reveals that racemic amlodipine is more efficacious than S-amlodipine in controlling B.P in the early weeks of study but at 12 weeks both the study drugs are equivalent in efficacy. Our study thus proves that S-amlodipine2.5mg is equally efficacious in reducing B.P compared to racemic amlodipine 5mg as evidenced by other studies [8]. This equivalent efficacy was noticed at 12 weeks in our study but earlier in other studies [16,17,18,19,20].

The appearance of ankle edema, the common adverse effect encountered with DHP-CCBs was assessed in our study by serial measurement of ankle circumference. Since the measurement of ankle circumference with measuring tape showed a higher reliability and feasibility in the outpatient set up than the other methods used for measuring peripheral edema, this method was chosen [21]. The racemic amlodipine group showed a significant increase in ankle circumference at 2,6and12 weeks from baseline ($p=0.01,0.008$ &0.005respectively), with no significant increase in S-amlodipine group from baseline (at12 weeks, $p=0.15$). Various clinical trials done independently and in comparison with other CCBs, have cited that there is increased incidence of peripheral edema with this drug [22,23].

Comparison between the study groups showed a statistically significant increase in ankle circumference in racemic amlodipine group than S-amlodipine group at 2,6 and12 weeks ($p=0.009$, 0.007 & 0.009 respectively). Similar results have been obtained from other studies showing the higher incidence of ankle edema with racemic amlodipine compared to S-amlodipine [8,20]. The ankle edema was determined objectively by serial measurements in our study and was categorized as mild [24]. 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. An alternative cause for this lesser incidence could also be due to the lesser efficacy of the drug in early weeks compared to racemic amlodipine. Contradictory reports regarding ankle edema due to S-amlodipine have been given by a study from Nepal [25].

Two studies mention about a significant increase in the liver enzymes, AST and ALT with both S-amlodipine and racemic amlodipine. But in our study there were no statistically significant alterations in liver function tests among the study groups [20,21]. The other laboratory parameters assessed like serum cholesterol, blood sugar, renal function tests were also within normal limits. The subjective symptoms like flushing, palpitation and headache commonly associated with CCBs were not noticed in both the study groups.

In the view of above results and discussion, it has been shown that S-amlodipine 2.5mg is equally efficacious to racemic amlodipine 5mg in mild to moderate hypertension at 12 weeks, though the efficacy is less at 2and 6 weeks. The tolerability profile is also desirable with lesser incidence of ankle edema and other side effects that favors its use in long term therapy of essential hypertension.

This study being a short duration study, further long term studies could provide more appealing results regarding the side effect profile of S-amlodipine with respect to ankle edema and liver function tests, its efficacy and interaction with other antihypertensive drugs in combination.

CONCLUSION

We conclude that, S-Amlodipine 2.5 mg O.D is found to be equally efficacious when compared to Racemic Amlodipine 5 mg O.D in mild to moderate hypertension only after 12 weeks of therapy. S-Amlodipine 2.5 mg has a better tolerability profile in comparison to Racemic Amlodipine 5mg with respect to ankle edema but necessitates long duration studies in this regard.

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