



ORIGINAL ARTICLE

Comparative Effect of Racemic Amlodipine and its Enantiomer with Atenolol on Hypertensive Patients—A Randomized, Open, Parallel Group Study

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Background: The ultimate goal of hypertensive therapy is to maintain normal blood pressure. A combination therapy is emphasized in the guidelines as a possible tool of reducing blood pressure to the target level. In this context, a combination of amlodipine and atenolol was chosen. Amlodipine exists in RS-form and its enantiomer in S-form. This study aimed at evaluating the effectiveness of two forms of amlodipine combined with atenolol in hypertensive patients.

Methods: This was an unicenter, parallel-group, prospective, pilot study. Patients, aged between 18 years and 65 years, of either sex, and without comorbidities were included in this study. Patients were randomizedly allocated into two groups. Group 1 patients received atenolol 25 mg plus racemic (RS)-amlodipine 5 mg and Group 2 patients received atenolol 25 mg plus S-amlodipine 2.5 mg for a period of 6 months. Blood pressure was monitored at every predefined clinical visit.

Results: Totally 64 patients completed the study. No statistical difference was reported in the demographic details of study patients. A significant ($p < 0.05$) reduction was observed in both systolic and diastolic blood pressure after 160 days of treatment with RS-amlodipine and atenolol. The same result was demonstrated by S-amlodipine and atenolol treatment. No statistical significant difference was observed between RS-amlodipine and S-amlodipine. Nine adverse drug events were encountered during the study period.

Conclusion: No difference was observed between racemic RS- and S-amlodipine combined with atenolol in terms of clinical benefits. Both combinations were found to be effective in reducing blood pressure without affecting the patients adversely.

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1. Introduction

Hypertension is a major public health problem and a risk factor for coronary heart diseases and vascular diseases in the world. The goal of an antihypertensive therapy is to maintain the blood pressure below 140/90 mmHg.¹ However, many hypertensive patients cannot attain the target level of blood pressure with a single drug. Doubling or increasing the dose of a single drug may cause a number of potential side effects. Hence, this option is not preferred by most physicians. Therefore, adding a second drug with a complementary mechanism is a safer choice.² Combining the two drugs via different mechanisms of action produces either an additive or a synergistic action. Therefore, a combination therapy is emphasized

in the Joint Nation Committee (JNC-7) guideline as a good way of reducing blood pressure to the target level.³

A combination of a calcium blocker and a beta blocker is an attractive therapy regimen because calcium blockers act by relaxing the smooth muscle directly and beta blockers act by the baroreceptor mechanism.⁴ Apart from this, beta blockers tend to control reflex tachycardia caused by calcium channel blockers, and at the same time, calcium channel blockers may enhance the tendency of beta blockers to increase peripheral vascular resistance.⁵ In this study, we chose amlodipine and atenolol, which are a calcium channel blocker and a beta blocker, respectively.

Chiral switching is an important concept in drug development. In the racemic mixture, one enantiomer may either be inactive or potentially have variable activity compared to other enantiomers. Amlodipine isomers exists in R(+) and S(−) forms, and synthetic amlodipine in racemic RS-form. Although racemic amlodipine contains both R- and S-form, only S-form possesses therapeutic action. Calcium channel blocking activities of S-form are a thousand

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times more potent than those of R-form. The dose of S-amlodipine is exactly half the dose of RS-amlodipine. Therefore, formulations containing only S-amlodipine have been developed. However, both RS- and S-form of amlodipine are available in the market.^{6–8}

Considering all the background information, we designed a study to evaluate the antihypertensive efficacy of combinations of racemic and S-amlodipine with atenolol in hypertensive patients. To the best of our knowledge, no study has so far been carried out in a South Indian population. This kind of a study in Indian population would help healthcare providers in choosing the appropriate medication to manage hypertension.

2. Methods

2.1. Ethical issues

The study was approved by the Institutional Ethical Committee (331/IEC/2012). The nature of the study and study medications were explained to the patients by the investigator orally, and an information brochure was prepared in Tamil language and issued to patients. Written consent was obtained from all the participants prior to the initiation of study procedure.

2.2. Study design and patient recruitment

The study was undertaken at the General Medicine Department of SRM Medical College Hospital and Research Center, Kattankulathur, Tamil Nadu, India. This was an open-label, randomized, parallel-group, prospective, comparative study. A total of 64 patients completed the study. Patients, aged between 18 years and 65 years, of either sex, without comorbidities, and with physician-diagnosed hypertension were included in the study. Patients with a history of secondary hypertension, cardiac disorders, coronary artery bypass surgery, or any ischemic attack in the past 6 months; pregnant women and lactating mothers; and those with significant hepatic and renal dysfunction and voluntary withdrawal were excluded from the study. Patients with a known history of hypersensitivity to any of the study medications were not enrolled in the study.

2.3. Study protocol

Patients satisfying the above mentioned study criteria were enrolled in the study, and were randomized using a randomization chart generated by a computer-assisted random allocation procedure. The randomization chart was prepared by a third person who was not involved in the study. Allocation was concealed using serially numbered, opaque envelopes.

Patients were divided into two groups: Group 1 ($n = 32$) and Group 2 ($n = 32$). Clinical information relevant for the study was collected from the patients, healthcare professionals, necessary records, as well as patients' bystanders in few cases. Other antihypertensive drugs, if being received by any patients, were stopped for a period of 7 days (run-in period) prior to the study. Patients who were in Group 1 received atenolol 25 mg (Ziblok-25, FDC Ltd, Mumbai, India) plus RS-amlodipine 5 mg (Amlokind, Mankind Pharma Ltd, New Delhi, India) and Group 2 patients received atenolol 25 mg plus S-amlodipine 2.5 mg (S-Numlo-2.5, Emcure Pharmaceutical Ltd, Hinjawadi, Pune, India) for a period of 6 months. The drugs were administered orally once daily in the morning. Patients were asked to bring their tablet strips at each study visit and instructed to maintain the given medication record diary. Patient compliance with study medication was assessed with the above tools at their clinic visits.

All the patients' blood pressure and clinical symptoms were measured at the baseline and on all follow-up days, i.e., Days 30, 60,

90, 120, 150, and 180. At each and every follow-up, patient medication adherence was monitored. Blood pressure was measured twice at 5-minute intervals in the same arm, with the patient being in a sitting position, using a mercury sphygmomanometer; prior to measuring the blood pressure, patients were asked to take a rest for at least 10 minutes. If the difference between two blood pressure values exceeded 5 mmHg, measurements were repeated until reproducible consecutive measurements were obtained.

2.4. Statistical analysis

Being a pilot study, a sample size of not less than 30 in each group was considered in order to reject the null hypothesis. A dropout rate of 20% was considered. Data [expressed as mean $\pm$ standard deviation (SD)] were entered into the Epi Info software. Probability values of less than 0.05 were considered for statistical significance. Demographic characteristics such as age, gender, baseline, and final visit data were used to assess response rates by comparing both groups. Student *t* test was used for comparison within groups. One-way analysis of variance Bonferroni multiple comparison test was used for comparing between groups (GraphPad Software, Inc., La Jolla, CA, USA).

3. Results

A total of 97 patients attended the screening phase for mild to moderate hypertension condition, out of which 84 patients met the study criteria. Patients who got enrolled after giving informed consent were randomized into two groups to receive study medications. A flow chart representing patient distribution is illustrated in [Figure 1](#).

In Group 1, out of 32 patients, 17 were male and 15 were female; their mean age was 54.18 ± 3.7 years and mean body mass index (BMI) was 30.6 ± 2.4 . Out of 32 patients in Group 2, 14 were male and 18 were female, having a mean age of 55.28 ± 6.8 years and mean BMI of 30.8 ± 3.1 . No significant difference was observed in age and BMI between the study groups ([Table 1](#)).

In Groups 1 and 2, respectively, 21.9% ($n = 7$) and 28.1% ($n = 9$) patients were found to be coolies; 15.6% ($n = 5$) and 12.5% ($n = 4$) were employed; 12.5% ($n = 4$) and 12.5% ($n = 4$) were self-employed; none and 3.1% ($n = 1$) were professional; and 34.4% ($n = 11$) and 31.3% ($n = 10$) fall into other categories, including housewives, etc. Educational status of the patients is also shown in [Table 1](#): 43.8% patients in Group 1 and 46.9% in Group 2 were illiterate; 25% ($n = 8$) in Group 1 and 28.1% ($n = 9$) in Group 2 studied between first and 10th standard; 31.3% ($n = 10$) in Group 1 and 21.9% ($n = 7$) in Group 2 had an education between 11th standard and a basic degree; and none in Group 1 and 3.1% ($n = 1$) in Group 2 had postgraduation qualification.

Changes in the systolic and diastolic blood pressures (SiBP and DiBP) from baseline (Day 0) to the end of the study (Day 160) in both groups are shown in [Table 2](#). It is evident from the results that blood pressure values were reduced gradually at every follow-up. In both groups, no significant reduction in SiBP was observed on Day 30. From Day 60 onward, SiBP reduced statistically. However, DiBP reduced statistically in both groups from Day 30 onward.

Changes in SiBP ranged from 162 mmHg to 122 mmHg and those in DiBP ranged from 112 mmHg and 84 mmHg at different time intervals in the atenolol plus RS-amlodipine group, whereas in the atenolol plus S-amlodipine group, SiBP ranged from 164 mmHg to 124 mmHg and DiBP from 116 mmHg to 82 mmHg, as shown in [Table 2](#). Comparing blood pressures between Day 0 and Day 160, significant ($p < 0.05$) reductions in SiBP and DiBP were observed in both S-amlodipine- and RS-amlodipine-treated groups after 160

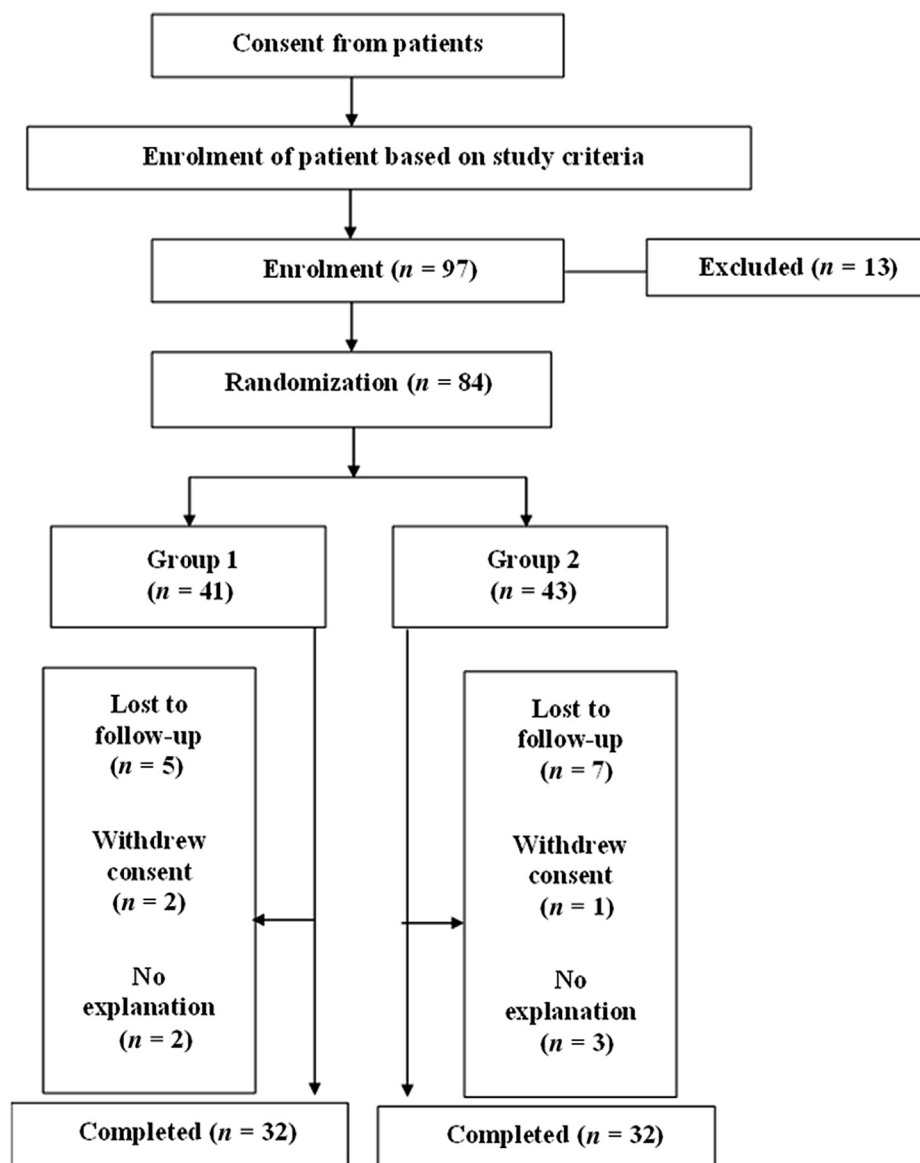


Figure 1 CONSORT diagram showing patient distribution. Group 1 received atenolol 25 mg (Ziblok-25, FDC Ltd, Mumbai, India) plus RS-amlodipine 5 mg (Amlkind, Mankind Pharma Ltd, New Delhi, India) and Group 2 patients received atenolol 25 mg plus S-amlodipine 2.5 mg (S-Numlo-2.5, Emcure Pharmaceutical Ltd, Hinjewadi, Pune, India) for a period of 6 months.

days of treatment. The mean difference in DiBP was 34 and 28, respectively, in Group 1 and 2, whereas that in SiBP was 40 with a confidence interval of 34.22–45.78 for both groups. No statistically significant difference was observed between RS- and S-amlodipine groups.

Safety and tolerability of study medications were assessed by physical examinations including heart rate measurements. In such assessments recorded in all the clinical visits, no significant changes were found compared to baseline values. Intercurrent illness, such as fever and seasonal infections, detected during the study period as a part of the safety assessment also did not have any major impact. No patients withdrew their consent from the study due to adverse events. According to Naranjo's Scale, a panel of judges confirmed that most of the adverse drug events were possibly related to study medications. Seven patients (21.9%) in Group 1 and 10 patients (31.3%) in Group 2 experienced a total of nine adverse drug events (Table 3).

4. Discussion

Hypertension is the most common cause of hospital visits and it is the routine diagnosis during their clinic appointments for any sort of problem. Hypertension is the main culprit in the progression of cardiac failure, cerebrovascular disease, ischemic heart disease, and renal failure. By maintaining normal blood pressure, all the above events can be controlled.⁹ Combinations of beta blockers and calcium channel blockers are commonly used antihypertensive drugs. Calcium blockers are vasodilators and increase plasma rennin levels, which is counterbalanced by beta blockers. Such combination drugs have one more benefit: side effect of each drug is neutralized by the other.^{5,10}

RS-amlodipine controls blood pressure by inhibiting the L-type calcium channel in cell membranes. S-amlodipine also has this activity, but R-amlodipine does not. This is the reason why the dose of S-amlodipine used is half the dose of RS-amlodipine.^{7,11}

Table 1 Demographic data of patients

Demographic variables	Atenolol plus RS-amlodipine (n = 32)	Atenolol plus S-amlodipine (n = 32)
Age (y)	54.18 ± 3.7	55.28 ± 6.8
BMI	30.6 ± 2.4	30.8 ± 3.1
Gender		
Male	53.1 (17)	43.8 (14)
Female	46.9 (15)	56.2 (18)
Socioeconomic status		
Coolie	21.9 (7)	28.1 (9)
Employed	15.6 (5)	12.5 (4)
Self-employed	12.5 (4)	12.5 (4)
Business	15.6 (5)	12.5 (4)
Professional	0 (0)	3.1 (1)
Others	34.4 (11)	31.3 (10)
Educational status		
Illiterate	43.8 (14)	46.9 (15)
1 st –10 th standard	25 (8)	28.1 (9)
11 th standard to degree level	31.3 (10)	21.9 (7)
>Degree	0 (0)	3.1 (1)

Data are presented as mean ± SD or % (n).

BMI = body mass index.

Ling et al¹² studied the effect of a combination therapy of atenolol and amlodipine on blood pressure control and concluded that a significant synergism exists between atenolol and amlodipine in stabilizing and lowering blood pressure. However, the study was a preclinical model. Pareek et al¹¹ observed the efficacy and tolerability of a fixed-dose combination of extended-release metoprolol and amlodipine in hypertensive patients in an open-label study. Kang et al¹³ compared the efficacy and safety profile of the amlodipine 5 mg/losartan 50 mg fixed-dose combination and amlodipine 10 mg monotherapy in hypertensive patients. Kim et al¹⁴ studied the efficacy and safety of S-amlodipine and racemic amlodipine in Korean hypertensive patients. Pathak et al¹⁵ conducted a clinical trial of S-amlodipine 2.5 mg versus amlodipine 5 mg in the treatment of patients with mild to moderate hypertension.

All these studies were carried out for a period of 8–12 weeks. With this background, 180-day duration of the present study was considered to be relatively sufficient to identify the effectiveness of study medications. However, the limitation of this study is that it did not measure the chronic effect of the combination therapy on blood pressure control.

This is the first clinical study in a South Indian population to evaluate the efficacy and safety profiles of racemic amlodipine versus and S-amlodipine. This study was designed as an open-label study. This may be a weakness of this study; however, in routine clinical practice, blinding of a drug may not be appropriate and the data obtained are suitable for real-life settings.

Table 2 Visit-wise changes in blood pressure

Baseline and follow-up	Blood pressure (SiBP/DiBP, mmHg)			
	Atenolol plus RS-amlodipine		Atenolol plus S-amlodipine	
	SiBP	DiBP	SiBP	DiBP
Day 0	162 ± 8.32	112 ± 7.68	164 ± 7.85	116 ± 8.57
Day 30	158 ± 8.15 (n.s.)	102 ± 8.47*	160 ± 6.17 (n.s.)	104 ± 6.98*
Day 60	152 ± 7.95*	99 ± 7.29*	150 ± 6.95*	98 ± 7.45*
Day 90	146 ± 7.52*	99 ± 7.48*	146 ± 7.34*	97 ± 6.68*
Day 120	141 ± 6.58*	96 ± 6.39*	142 ± 8.34*	94 ± 7.58*
Day 150	138 ± 6.59*	92 ± 6.47*	136 ± 8.42*	92 ± 8.25*
Day 180	122 ± 7.58*	84 ± 7.58*	124 ± 7.68*	82 ± 6.47*

Data are expressed as mean ± SD; Day 0 versus Days 30, 60, 90, 120, 150, and 180 in both groups.

*p < 0.05 in decreasing blood pressures; two-way ANOVA.

ANOVA = analysis of variance; DiBP = diastolic blood pressure; n.s. = not significant between the trial groups; SD = standard deviation; SiBP = systolic blood pressure.

Table 3 Adverse drug events in study patients

Sl. no.	Adverse events	Atenolol plus RS-amlodipine, n (%)	Atenolol plus S-amlodipine, n (%)
1	Facial flushing	1 (3.1)	1 (3.1)
2	Dizziness	—	1 (3.1)
3	Headache	1 (3.1)	3 (9.4)
4	Palpitation	2 (6.3)	1 (3.1)
5	Pedal edema	1 (3.1)	2 (6.3)
6	Fatigue	1 (3.1)	—
7	Cough	1 (3.1)	—
8	Nausea/vomiting	—	1 (3.1)
9	Skin eruption	—	1 (3.1)

In the present study, calcium blockers were used in combination with beta blockers for better control of hypertension. However, other similar studies^{14,15} used only calcium channel blockers. No great difference was found with respect to cost between RS- and S-amlodipine. Finally, this preliminary study concludes that combinations of atenolol 25 mg plus RS-amlodipine 5 mg and atenolol 25 mg plus S-amlodipine 2.5 mg were found to be clinically similar in reducing blood pressure, and no significant difference was observed with respect to efficacy and safety between these therapies.

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