Original Article

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A Randomized Open-Label Parallel-Group Study Evaluating the Efficacy and Safety of Candesartan Cilexetil and Amlodipine in Mild to Moderate Essential Hypertensives in a Tertiary Care Hospital in Chennai

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Abstract:

Objective: This research compared the effectiveness of combining amlodipine and candesartan in treating mild to moderate hypertensive patients. It suggests using drugs from different groups to achieve target blood pressure levels, as per contemporary evidence-based medicine. Hypertension is a leading global health threat, causing early deaths and other health conditions.

Materials and Methods: Newly diagnosed essential hypertensives with BP ≥140/90 to <180/110 mmHg were screened for this randomized, prospective, open-label, 3-arm, interventional, phase IV study. Eligible patients were divided into 3 groups, with amlodipine or candesartan cilexetil as monotherapy in 2 arms and the third arm with amlodipine + candesartan for 12 weeks. All the efficacy parameters will be presented as a percentage change in the mean of blood pressure from baseline and were compared using ANOVA with p-value<0.05 to be statistically significant.

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Results: Out of 90 patients randomized, 83 were included for analysis. While the reduction in systolic blood pressure by amlodipine, candesartan, and amlodipine + candesartan from baseline was 11.7, 13.1, and 19mm Hg, the reduction in diastolic blood pressure by amlodipine, candesartan, and amlodipine + candesartan was 6.2, 10.7 and 11.9 mmHg at the end of 12 weeks (p-value<0.0001). Out of a total of 90 participants in the 3 groups, the incidence of adverse events was reported by 7 participants.

Conclusion: The study found that combining a calcium channel blocker and an angiotensin receptor blocker was more effective and tolerable in treating mild to moderate essential hypertensives.

Keywords: amlodipine, candesartan cilexetil, hypertension, open-label parallel-group study

Introduction

Elevated blood pressure, also known as hypertension, poses a significant global public health challenge, particularly in countries with less developed healthcare systems. There are 4 categories of blood pressure: normal, prehypertension, Stage 1 hypertension, and Stage 2 hypertension. Each category is defined by specific ranges of systolic and diastolic blood pressure (SBP and DBP) measurements. While hypertension often does not present symptoms in its first stages and often goes undetected, there are substantial health and economic benefits associated with early identification, appropriate treatment, and the effective management of hypertension[1]. According to the latest AHA-2017 guidelines, it is recommended to start and continue treatment for hypertension with thiazide-type diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). These medications can be prescribed either individually or in combination, depending on the specific type and stage of hypertension. The given text is a list containing elements 1 and 2. There are 2 distinct levels that categorise the treatment objectives for blood pressure. For individuals at a low to moderate risk of hypertension, it is important to keep their blood pressure below 140/90 mmHg. For individuals who are at a higher risk of hypertension, such as those with diabetes, cerebrovascular disease, cardiovascular disease, or renal illness, it is recommended to aim for a blood pressure level below 130/80 mmHg[1,2].

Recent clinical trials have shown that using a single medication to control hypertension was not successful in the majority of patients, particularly those with other health conditions. Achieving the desired blood pressure goal usually requires using multiple medications, either in the form of fixed-dose combinations or by adding drugs one after another. Nevertheless, the choice of combination antihypertensive medication was determined by the ease of use and the ability to adjust the dosage as needed. There are various factors that contribute to high blood pressure. By combining agents with distinct and complementary mechanisms of action, it is possible to effectively inhibit pressor mechanisms and reduce the activation of counter-regulatory mechanisms. Using both components together as a therapy results in a more significant decrease in blood pressure than using either one alone[3,4].

Amlodipine is a prolonged-acting dihydropyridine, which is a kind of medication that dilates the peripheral arteries. It works by directly affecting the smooth muscles in the blood vessels, leading to a decrease in resistance in the peripheral blood vessels and a subsequent decrease in blood pressure[5]. Candesartan is an angiotensin receptor II

blocker that has a much higher attraction (>10,000 times) to the angiotensin receptor I. By interacting with the receptor, it effectively blocks the binding of angiotensin II, which in turn prevents the negative effects of vasoconstriction and aldosterone secretion caused by angiotensin II. When a specific type of calcium channel blocker called dihydropyridines is used in combination with an ACE inhibitor or ARB, it can help reduce the occurrence of abnormally fast heart rate (tachycardia) that may happen during therapy. This is due to the antisympathetic effects of these medications. In addition, RAAS inhibitors somewhat counteract peripheral oedema resulting from arteriolar dilatation, which is a side effect of these CCBs that limits the dosage. The purpose of this research was to evaluate the effectiveness, safety, and tolerability of combining the medications amlodipine and candesartan (an ARB and CCB, respectively) and to compare the results with using either drug alone in individuals with mild to moderate hypertension[6-8].

Material and Methods

The study took place at the outpatient Department of General Medicine, Sri Ramachandra Hospital from June 2013 to August 2013. The study lasted for 12 weeks and involved 3 different treatment groups. It was a randomised and open-label study with active control. The participants were divided into parallel groups. This study was conducted in Phase 4. The study was granted approval by the Institutional Ethics Committee (IEC No: CSP-MED/12/OCT/04/38) of Sri Ramachandra Medical College & Research Institute, Sri Ramachandra University. The research was conducted following ethical guidelines and informed consent was obtained from each participant before their involvement in the study. The participants for the study were chosen based on the judgement of the treating physician.

This study enrolled participants aged 18 to 65 of any gender who had recently been diagnosed with mild to moderate essential hypertension. The participants exhibited systolic blood pressure (SBP) ranging from 140 to 160 mmHg, along with diastolic blood pressure (DBP) ranging from 88 to 96 mmHg. Participants were asked to give written consent and commit to being present for the entire duration of the study. People with a documented medical history of various significant diseases or conditions were excluded from the study. Individuals who had a documented history of alcohol, drug, or opioid misuse, were taking other medications at the same time, or had a known sensitivity to the substances being studied were not included as participants. Additionally, females who were pregnant or breastfeeding or had the ability to bear children but had been surgically sterilised for less than one year were also excluded. Furthermore, females who were under the age of 50 and had entered menopause within the past 24 months before the screening visit, as well as those who were noncompliant or uncooperative during the study according to the investigator's knowledge, were excluded.

Study settings

Individuals who completed the first assessment and satisfied the requirements for participation were registered from the Out-Patient Department of Medicine, Sri Ramachandra Medical College & Research Institute, Sri Ramachandra University. The sample size required to conduct the study was calculated from the anticipated difference in mean of decrease in SBP (mmHg) between the 3 groups of 1.41 using previous studies along with 80% power, α- error of 5%, and 10% dropout rate found to be around 90 by the statistician, 30 in each arm with Group- I, II, III receiving amlodipine (2.5 mg), candesartan (8 mg) tablets and amlodipine 5 mg + candesartan 8 mg once daily in the morning after breakfast respectively. The participants were randomized using a simple randomization

method using a Random Number Table and allocation concealment was done using the SNOSE method. Since it was an open-label study, the participants were aware of the drugs given to them. The investigator obtained the research medications from the hospital's pharmacy and provided them at no charge. The trial therapy lasted for a total of 12 weeks, followed by a 2-week period for observation. Participants were required to attend 3 specific time points throughout the research, 3 days before randomization, at randomization, and 4 weeks after beginning the study medication. Additionally, participants were required to attend a follow-up visit at 12 weeks, which marked the conclusion of the study drug usage, and another visit 2 weeks after stopping the study medication. After 12 weeks of taking the study medicine, the treating physician conducted a follow-up with the subjects. The decision to discontinue medication treatment was made by the doctors, who relied on their clinical assessment.

Study procedure

During the first visit, a case report form with demographic details, medical screening that included complete clinical evaluation (medical history, physical examination, record of height, weight, and vital signs), and laboratory investigations of LFT, RFT, ECG, and chest X-ray and informed consent of the patient was obtained and documented. The physician decided upon the enrolled participant's eligibility criteria, randomized to treatment groups by dispensing the study drugs to them, and also advised them to take the drug according to the protocol and contact the physician if any adverse event occurred during the second visit. During the subsequent visits, the primary and secondary endpoints were assessed till the termination of the study. The BP measurements were conducted using a validated Mercury sphygmomanometer (Diamond BD 112) between 08.00 and 10.00 AM. Prior to the measurements, participants were required to abstain from consuming caffeine, engaging in physical activity, or smoking for at least 30 minutes. The participants were directed to assume a sitting position with both feet aligned in a parallel manner and resting flat on the floor. It was assured that the subject remained sat for a minimum of 5 minutes prior to the commencement of the first measurement. Two readings of BP were taken with a gap of 4-5 minutes and if the 2 readings did not differ by more than 5%, the mean of the 2 was taken as the BP reading; if the difference was more than 5%, a third reading was taken and the mean of the nearest 2BP readings was the final BP. Compliance was assessed by pill count at every visit.

Efficacy assessment

The main objective was to measure the reduction in average systolic blood pressure while sitting, from the beginning of the therapy to the conclusion of the 12-week period. The secondary objectives included a reduction in average diastolic blood pressure compared to the first measurement, as well as an enhancement in tolerability, measured by a decrease in the number of reported adverse events.

Safety assessment

For safety evaluations, various measures were taken, including monitoring for any adverse events (AEs), conducting clinical laboratory exams (such as chemistry, haematology, and urinalysis), measuring vital signs (like sitting blood pressure and heart rate), performing physical examinations, and obtaining 12-lead electrocardiographs. Lab tests were conducted at various points during the research process, including before screening and at specific intervals. These intervals included days 0, 3, and weeks 2, 12, and 14. The researchers assessed and documented the seriousness of negative occurrences (mild, moderate, or severe) and their connection to the treatment (definitely related, probably related, potentially related, unlikely to be connected, or not related to the study medication) based on their evaluation.

Statistical analysis

The statistical analysis was conducted using Sigma GraphPad Software, version 4 from the USA. Variables that follow a normal distribution are typically expressed as the mean plus or minus the standard error (SE). Non-parametric data were represented as frequencies (percentages). Intention-to-treat (ITT) analysis was used for all the statistical analysis. Baseline intergroup comparability concerning demographic variables and efficacy parameters was assessed. Intergroup and comparison of baseline parametric and non-parametric data was done by unpaired t-test and Chi-square test, respectively. Within and between group analysis of the symptoms and signs scores, and quality of life scores was performed using repeated measures ANOVA. For statistical significance, a probability value of less than 0.05 will be considered.

Results

Study population

A group of 100 individuals who had recently been diagnosed with essential hypertension and had blood pressure readings within a specific range were carefully examined. Out of them, 10 did not give informed consent and were ineligible for our study. The 90 participants were then randomized to the 3 treatment groups: Group A – amlodipine 5 mg, Group B- candesartan 8 mg, and Group C- amlodipine 2.5 mg + candesartan 8 mg with 30 in each group. A total of 7 participants dropped out of the study (2 from the amlodipine group, 2 from the candesartan group, and 3 from the combination therapy). Therefore, 83 participants completed the 12-week treatment period along with the 2-week follow-up periods and were considered for analysis (Figure 1).

The initial demographic and clinical parameters of the 3 groups, such as age, gender, weight, height, body mass index, smoking habits, alcohol consumption, prevalence of diabetes, and baseline blood pressure, were not substantially different (p-value>0.05) (Table 1).

Efficacy analysis

After 12 weeks of treatment with the study drugs, the reduction in mean SBP from baseline by all 3 groups was significant. (p-value<0.05). In the amlodipine group, baseline mean SBP was 149.6±4.76 and 137.7±7.00 mmHg, and after 12 weeks of treatment reduced to mmHg (p-value<0.05). In the candesartan group, the reduction in mean SBP was again significant with the baseline mean SBP of 150.7±3.69 mmHg and after 12 weeks of treatment reduced to 137.6±5.54 mmHg. In the amlodipine (2.5 mg) + candesartan (8 mg) group, with the baseline mean SBP of 152.3±4.22 mmHg and SBP at the end of treatment, the reduction was found to be again significant. When the between-group analysis was done using ANOVA, the SBP reduction was greater in the combination group than in the other monotherapy groups (p-value<0.05) (Table 2).

The baseline mean DBP of all 3 groups was similar. In the amlodipine group, the baseline mean DBP was 91.7±2.78 mmHg, and after 12 weeks of treatment reduced to 85.5±2.50 mmHg (p-value<0.001). In the candesartan group, the reduction in mean DBP was again significant, with the baseline mean DBP of 93.1±2.54 mmHg and, after 12 weeks of treatment, reduced to 82.4±2.31 mmHg (p-value<0.001). In the amlodipine (2.5 mg) + candesartan (8 mg) group, with the mean baseline DBP of 92.1±2.57 mmHg and DBP at the end of treatment of 80.2±2.31 mmHg, the reduction was found to be again significant (p-value<0.0001). When the between-groups analysis was done, the difference was not significant (p=0.0872), proving that the effects of treatment with amlodipine, candesartan, and amlodipine/candesartan in terms of reduction in DBP after 12 weeks were similar (Table 3).

Safety analysis

The total occurrence of AEs was rather low and did not show any meaningful variation across the 3 treatment groups. Among the 90 participants in the 3 groups, 7 persons reported experiencing adverse effects. There was a total of 2 dropouts in the Amlodipine group due to headaches in one person and occasional palpitations in another participant. Two had mild headaches with candesartan 8mg and withdrew from the study. In amlodipine (2.5 mg) + candesartan (8 mg) once a day, 3 participants had adverse events, one with dizziness and another with a moderate headache. One participant withdrew consent to participate in the study in the amlodipine (2.5 mg) + candesartan (8 mg) group without giving any reason (Figure 2).

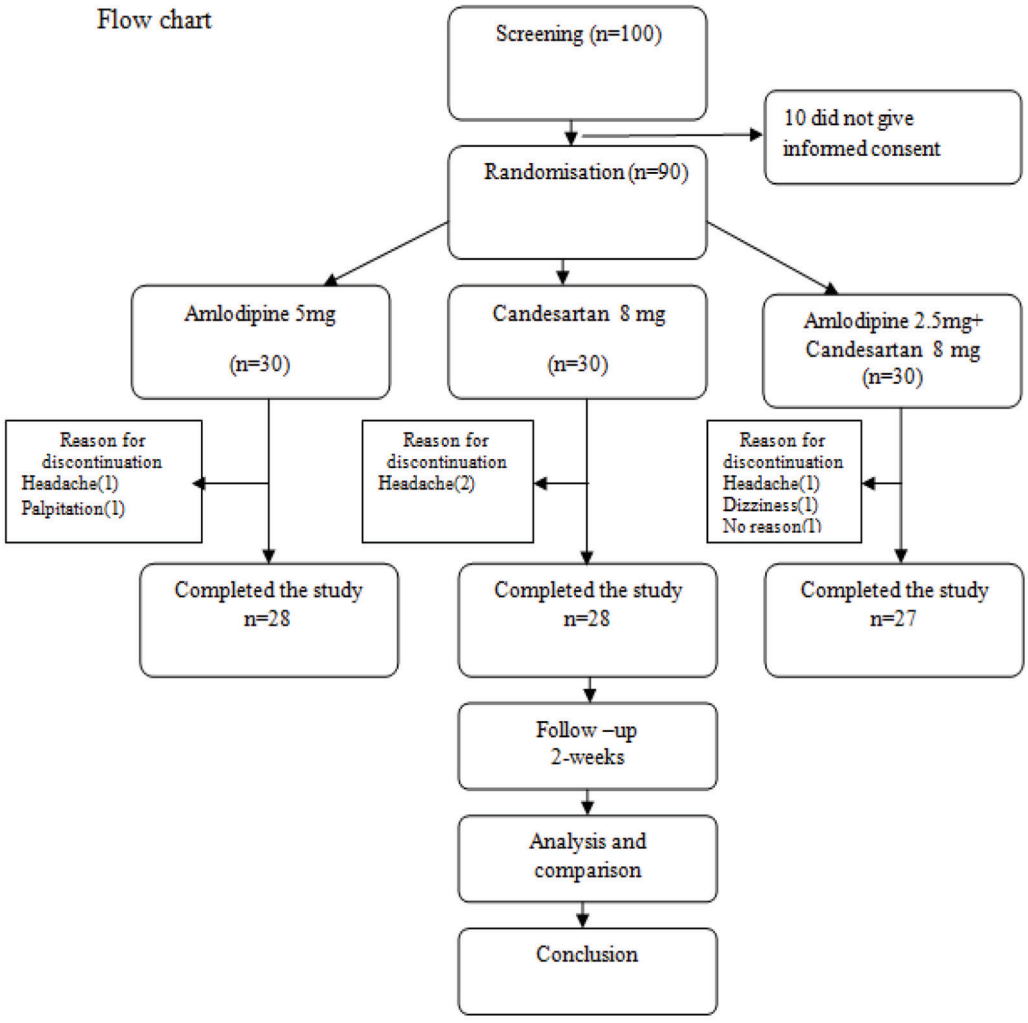

Figure 1 CONSORT Flow chart: 90 participants completed the 12–week treatment period, as well as 2 follow–up periods, and were considered for analysis

Table 1 Baseline characteristics of participants

Characteristic	Amlodipine 5 mg once a day	Candesartan 8 mg once a day	Amlodipine (2.5 mg) + Candesartan (8 mg) once a day
Age (years)	45.3±7.69	47.6±6.98	44.5±7.06
Male: Female	23:07	21:09	20:10
Height (cm)	161.2±9.53	159.5±12.47	161.7±11.05
Weight (kg)	61.9±7.9	60.2±9.08	62.2±9.08
BMI (kg/m^2)	23.8±0.85	23.6±1.40	22.9±1.69
Type 2 Diabetes Mellitus	08	11	07
Alcoholics	09	07	09
Smokers	6	8	10

*All values are mean±standard deviation. n=30/group, BMI=body mass index

Table 2 Impact on average systolic blood pressure following 12 weeks of the treatment

Group	Systolic blood pressure	
	Baseline	After 12 weeks of treatment
Amlodipine-5 mg, once a day	149.6±4.76	137.7±7.00*
Candesartan-8 mg, once a day	150.7±3.69	137.6±5.54*
Amlodipine (2.5 mg) + Candesartan (8 mg) once a day	152.3±4.22@	133.3±3.88#

*p=value<0.0001, @p-value<0.05 and #p-value<0.0001.

Table 3 Effect on mean diastolic blood pressure after 12 weeks of treatment

Group	Diastolic blood pressure	
	Baseline	After 12 weeks of treatment
Amlodipine-5 mg, once a day	91.7±2.78	85.5±2.50*
Candesartan-8 mg, once a day	93.1±2.54	82.4±2.31*
Amlodipine (2.5 mg) + Candesartan (8 mg) once a day	92.1±2.57@	80.2±2.31*#

*p-value<0.0001, @p-value<0.05 and #p-value<0.0001.

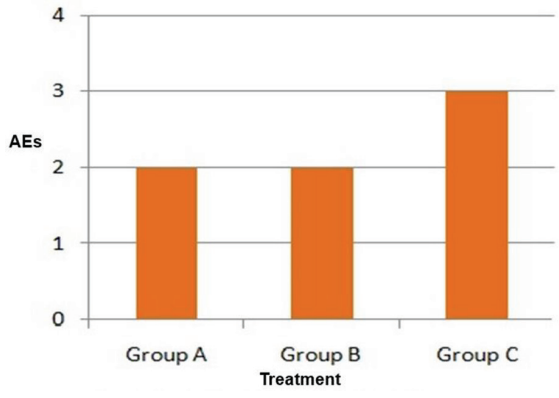

Figure 2 Incidence of adverse events after 12 weeks of the treatment. Group A- amlodipine 5mg once a day, group B- candesartan 8mg once a day, and group C- amlodipine 2.5 mg + candesartan 8mg once a day. AEs- adverse events

Discussion

In this study, patients with mild to moderate hypertension were divided into 3 groups. Two groups received monotherapies with amlodipine 8 mg and candesartan, while the third group received a combination therapy of amlodipine and candesartan. At the end of the 12 weeks, all 3 groups experienced a notable decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP). However, the reduction in the mean SBP by the combination therapy with amlodipine/candesartan was found to be significant when compared between the monotherapy groups. Also, the adverse events reported by both the monotherapy and combination therapy were only mild, leading to just 6 out of 90 patients who discontinued their participation in the study.

It is recommended to use thiazide diuretics, beta-blockers, calcium antagonists, ACEIs, and ARBs to initiate and sustain antihypertensive treatment, according to the current guidelines. These medications can be used alone or in combination, depending on the presence of other conditions. ACEIs and ARBs are commonly prescribed for managing high blood pressure. They are particularly effective in reducing the occurrence of hypertension-related consequences, including stroke, heart attack, heart failure, and even death[9,10]. Abraham HM et al. compiled a comprehensive collection of relevant research studies that compared the antihypertensive effects and cardiovascular advantages of ARBs, while also addressing safety and tolerability concerns[11]. A SCOPE study has also shown the effectiveness and safety of candesartan in individuals with hypertension[12]. In several studies, the CCB category of medicines was shown to be either non-inferior or superior to ARBs and ACEIs[13,14]. A clinical investigation, known as the VALUE trial, conducted to assess the effectiveness of amlodipine compared to valsartan, found no significant differences in the reduction of cardiovascular morbidity or death among hypertensive patients[15].

The clear benefit of starting treatment with monotherapy is the use of a single medication, allowing for the attribution of both the efficacy and bad effects of that specific medication. A potential drawback is that if using only one medication proves to be unsuccessful or not effective enough, finding a different medication that is more effective or better tolerated can be a time-consuming process, which may discourage adherence[16]. Extensive analysis of more than 40 trials has revealed that when 2 agents from different families of antihypertensive medications are combined, there is a significantly greater reduction in blood pressure compared to simply increasing the dosage of a single agent[17]. Starting a dual-drug combination for hypertension treatment has been found to lower the chances of stopping the medication. Another advantage of this approach is a notable reduction in blood pressure for individuals with extremely high blood pressure, rapid control of blood pressure (especially for patients at high risk of cardiovascular issues), and minimal adverse effects. Most recommendations suggest using an ACEI or ARB, along with a thiazide diuretic or a CCB. Through a comprehensive analysis, it was discovered that when 2 different antihypertensive medications are combined, there is a significant decrease in blood pressure compared to simply increasing the dosage of a single drug. Interestingly, the decrease in blood pressure can be significantly greater when 2 agents are utilised, as opposed to simply increasing the dosage of a single agent[18-21].

The justification for using a combination of medications that inhibit the RAAS together with a CCB or diuretic is well-established. Nevertheless, the use of ARBs and CCBs provides additional advantages other than reducing blood pressure. These benefits include improvements in the occurrence of diseases and death rates in individuals with hypertension and other accompanying medical disorders[22-24]. A study conducted by Calhoun et al. found that combining valsartan and amlodipine resulted

in better effectiveness and tolerance in individuals with hypertension, compared to using either medication alone[25]. A recent study conducted by Farsang et al. has shown that the combination of candesartan cilexetil and amlodipine is effective and well-tolerated among patients diagnosed with primary hypertension. They also found that this combination leads to a significant improvement in the antihypertensive impact, without compromising tolerance. This finding has substantial therapeutic implications[26]. A study conducted by Koyanagi et al. suggests that combining amlodipine and candesartan may be more beneficial in reducing cardiovascular events in hypertensive patients compared to other combination treatments with candesartan[27]. In line with our findings, our research showed similar results, except for the fact that the combination treatment proved to be more effective in lowering systolic blood pressure while maintaining the same level of effectiveness in reducing diastolic blood pressure. The pharmacological rationale for combining amlodipine (CCB) and candesartan (ARB) is that they work in different ways. Candesartan and ARBs block the angiotensin II receptor directly, which leads to the antagonism of angiotensin II at the vascular and myocardial levels. In contrast, amlodipine, a calcium antagonist, reduces vascular resistance by relaxing the smooth muscles in the blood vessels. In addition, the detrimental sodium imbalance induced by CCBs contributes to the blood pressure-lowering action of RAAS blockers. The occurrence of peripheral oedema caused by CCBs may be reduced when a RAAS blocker is present, and the extent of reduction may vary depending on the dosage[28-31].

The research was constrained by its brief duration of therapy and a very small number of participants. Furthermore, it is important to use care when interpreting the safety data. To ascertain the therapy's long-term safety and therapeutic consequences, a comprehensive investigation on a broad scale may be necessary.

Conclusion

A recent study conducted at the Department of Pharmacology in collaboration with the Department of Medicine, Sri Ramachandra Hospital, evaluated the safety and effectiveness of amlodipine and candesartan cilexetil as a single-drug therapy and in combination for individuals with recently diagnosed mild to moderate hypertension. The findings revealed that all 3 groups undergoing treatment witnessed notable decreases in blood pressure and a greater likelihood of reaching blood pressure goals, with minimal side effects. However, the simultaneous use of multiple treatments demonstrated that the combination of amlodipine and candesartan cilexetil was highly effective in treating mild to moderate essential hypertension. This suggests that utilising both an angiotensin receptor blocker and a calcium channel blocker together could be a more beneficial and safer treatment option.

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Conflict of interest

The authors declare no conflict of interest in the manuscript.

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