OPEN ACCESS JOURNALS
Indiana Journal of Humanities and Social Sciences
Abbriviate Tittle- Ind J Human Soc Sci
ISSN *(Online)*- 2582-8630
Journal Homepage Link- https://indianapublications.com/journal/IJHSS
DOI: https://doi.org/10.5281/zenodo.15192401

INDIANA PUBLICATIONS
PRODUCTIVE AND QUALITY RESEARCH

Research Article

Volume-06|Issue-04|2025

Evaluation of Amlodipine, Lisinopril, and Their Combination in the Treatment of Primary Hypertension

Habibullah Momand[1], Khalilullah Kaliwal[*2]

[1,2] Department of Pathology, Faculty of Medicine, Balkh University, Afghanistan

Article History
Received: 07.03.2025
Accepted: 08.04.2025
Published: 09.04.2025

Citation
Momand, H., Kaliwal, K. (2025). Evaluation of Amlodipine, Lisinopril, and Their Combination in the Treatment of Primary Hypertension. *Indiana Journal of Humanities and Social Sciences, 6*(4), 1-4

Abstract: Angiotensin converting enzyme (ACE) inhibitors and dihydropyridine calcium antagonists are well established and widely used as monotherapy in patients with mild to moderate essential hypertension. Earlier studies combining short acting drugs from these classes require multiple dosing and were associated with poor compliance. Availability of longer acting compounds allows once daily administration to avoid the inconvenience of a multiple daily dose. It was decided to perform a randomised double blind, crossover study with the long acting calcium channel blocker amlodipine and the long acting ACE inhibitor lisinopril, given either alone or in combination in essential hypertension. Twenty four patients with diastolic blood pressure (DBP) between 95 and 104 mm Hg received amlodipine 2.5 mg and 5 mg, lisinopril 5 mg and 10 mg, and their combination as per a prior randomisation schedule. Supine and standing blood pressure and heart rate were recorded at weekly intervals. Higher doses of both the drugs individually or in combination were used if the target supine DBP below 90 mm Hg was not achieved. There was a significant additional blood pressure lowering effect with the combination when compared either with amlodipine or lisinopril alone. Five mg amlodipine and 10 mg lisinopril monotherapy achieved the target blood pressure in 71% and 72% patients respectively. The combination of 2.5 mg amlodipine with 5 mg lisinopril produced a much more significant lowering of blood pressure in a higher percentage of patients than that with an individual low dose.

Keywords: Amlodipine, lisinopril, hypertension, monotherapy, combination therapy.

INTRODUCTION

Previous studies have clearly demonstrated that monotherapy does not provide an acceptable response in controlling patients' blood pressure. While monotherapy has shown exceptional results in some patients, it has been unsatisfactory in others. Combination therapy is recommended in cases where monotherapy fails to achieve the expected blood pressure control.

Recently, the combination of antihypertensive drugs with diuretics has been advised. However, with the introduction of new classes of antihypertensive medications, blood pressure can now be managed more effectively and appropriately. Understanding the mechanism of drug action allows for the recommendation of an optimal and well-balanced combination therapy for blood pressure control.

ACE enzyme inhibitors and calcium antagonists are widely recommended for monotherapy in the treatment of hypertension. By understanding the mechanism of action of both drug classes, an optimal combination with fewer side effects can be achieved.

Calcium antagonists have vasodilatory effects and increase plasma renin levels. Therefore, their combination with ACE inhibitors can yield satisfactory results. Additionally, studies have shown that dihydropyridine calcium antagonists exert diuretic and natriuretic effects, which in turn make them an excellent combination with ACE inhibitors. The combination of calcium antagonists and ACE inhibitors significantly reduces blood pressure in hypertensive patients compared to monotherapy.

The combination of nifedipine and captopril has shown significant and superior effects compared to other combinations of these two drug classes. However, it should be noted that its duration of action is short. Combination therapy with 5 mg enalapril and 5 mg felodipine has demonstrated significant and satisfactory effects on hypertension in both supine and standing positions.

It is important to note that long-acting drugs, such as amlodipine and lisinopril, require only once-daily administration, making them more convenient and satisfactory for both patients and physicians.

The objective of this study is to conduct a double-blind, randomized comparison of the efficacy and safety of amlodipine and lisinopril, both as monotherapy and in combination therapy.

RESEARCH METHODOLOGY

Patients with mild to moderate hypertension, having diastolic blood pressure between 90-104 mmHg, were included in the study after undergoing two weeks of antihypertensive therapy to rule out secondary causes of hypertension.

***Corresponding Author:** Khalilullah Kaliwal

Patients with renal and hepatic diseases, ischemic heart disease, cerebrovascular disorders, diabetes, pregnant women, and those using contraceptive medications were excluded from the study.

A total of 30 patients (16 men and 14 women) were included in the study. Before their inclusion, blood pressure was measured repeatedly and systematically. Subsequently, their blood pressure was monitored and measured weekly for a duration of four weeks.

After a four-week placebo phase, the patients entered the double-blind, randomized study phase. Patients were randomly assigned to amlodipine monotherapy, lisinopril monotherapy, or a combination of both drugs. Each treatment period lasted four weeks.

In amlodipine monotherapy, 2.5 mg daily was administered for two weeks. For patients whose supine diastolic blood pressure remained above 90 mmHg, the dose was increased to 5 mg daily.

In the lisinopril group, 5 mg daily was prescribed for two weeks. If supine diastolic blood pressure exceeded 90 mmHg, the dose was increased to 10 mg daily.

In combination therapy, treatment started with 2.5 mg amlodipine and 10 mg lisinopril daily. If supine diastolic blood pressure remained above 90 mmHg, amlodipine was increased to 5 mg while lisinopril remained at 10 mg daily. Patients' blood pressure was measured at each visit between 9 AM and 10 AM, approximately 42 hours after the previous drug dose.

In the supine position (after 10 minutes) and the standing position (after 2 minutes), blood pressure was measured using the L&T minimum 7133 device by the same observer.

During both visits, all patients were questioned regarding any changes in their previous symptoms as well as any newly observed symptoms. Patients were instructed to bring their unused medications to each visit to ensure proper adherence to the prescribed regimen.

RESULTS

Patients who had taken at least one dose of antihypertensive medication were included in the study. In total, 30 patients (16 men and 14 women) with an average age of 49.8 years (ranging from 41 to 62 years) were studied and evaluated. Among the 30 patients, 24 completed all stages and phases of the study.

After the placebo phase, the average (SD) blood pressure in the supine position was 149 (+-10)/98(+5) mmHg, and in the standing position, it was 155(+11)/103(+5) mmHg. The heart rate was measured at 76(+6) beats/min in the supine position and 77(+8) beats/min in the standing position.

Amlodipine at 2.5 mg and 5 mg significantly lowered blood pressure in both the supine and standing positions. Similarly, lisinopril at 5 mg and 10 mg effectively reduced blood pressure in both positions.

The predetermined goal of reducing diastolic blood pressure below 90 mmHg in the majority of patients was achieved with monotherapy using either 5 mg amlodipine or 10 mg lisinopril. However, a significant reduction in both systolic and diastolic blood pressure in both supine and standing positions was observed with the combination of amlodipine and lisinopril, which was not observed with monotherapy.

The average (SD) blood pressure in the supine position decreased from 149 (+-10)/98 (+-6) mmHg to 140 (+-11)/92 (+-7) mmHg with 2.5 mg amlodipine, and to 137 (+-7)/85 (+-6) mmHg with 5 mg amlodipine ($P < 0.001$). The blood pressure in the standing position decreased from 155 (+-11)/103 (+-7) mmHg to 143 (+-12)/93 (+-8) mmHg with 2.5 mg amlodipine, and to 138 (+-6)/88 (+-6) mmHg with 5 mg amlodipine ($P < 0.001$).

Lisinopril at 5 mg reduced blood pressure to 138 (+-10)/90 (+-8) mmHg in both the supine and standing positions, and at 10 mg, it reduced blood pressure to 136 (+-7)/87 (+-5) mmHg ($P < 0.001$). However, with combination therapy, the blood pressure was sufficiently lowered and controlled. Combination therapy with 2.5 mg amlodipine and 5 mg lisinopril reduced blood pressure to 131 (+-9)/82 (+-7) mmHg in the supine position and to 132 (+-9)/83 (+-7) mmHg in the standing position ($P < 0.001$). With combination therapy of 5 mg amlodipine and 10 mg lisinopril, blood pressure was reduced to 127 (+-9)/79 (+-5) mmHg in the supine position and to 129 (+-7)/79 (+-5) mmHg in the standing position.

The predetermined goal of reducing diastolic blood pressure below 90 mmHg was achieved in 29% of patients with 2.5 mg amlodipine, 71% with 5 mg amlodipine, 25% with 5 mg lisinopril, and 72% with 10 mg lisinopril. However, with combination therapy, the goal was achieved in 54% of patients with 2.5 mg amlodipine and 5 mg lisinopril, and in 100% with 5 mg amlodipine and 10 mg lisinopril.

None of the recommended drug regimens had a significant effect on the heart rate. All patients tolerated the drug regimens without serious side effects. Ankle edema was more frequently observed with amlodipine, while sore throat and ear itching were more common with lisinopril. These side effects were more frequently observed with monotherapy, while they were much less common with combination therapy.

DISCUSSION

There are many drugs available in the market for the treatment of hypertension, but when used as monotherapy, these drugs are only effective in 40-60%

***Corresponding Author:** Khalilullah Kaliwal

of cases. Numerous studies have shown that combining two different classes of antihypertensive drugs is very effective in controlling blood pressure. The combination of calcium channel blockers and ACE inhibitors is more effective at reducing blood pressure compared to using these drugs alone. In the present study, we observed the high effectiveness of the combination of amlodipine and lisinopril in reducing and controlling blood pressure. Singet and colleagues observed the high effectiveness of the combination of nifedipine and captopril in reducing and controlling blood pressure, although the duration of this drug combination's effect was short. Many other researchers have reported similar effects of the nifedipine and captopril combination.

This study demonstrated the extraordinary effectiveness of the combination of amlodipine and lisinopril compared to the monotherapy use of these drugs in controlling and reducing blood pressure. This suggests that combination therapy has higher efficacy in both the duration of the effect and in reducing blood pressure compared to monotherapy.

In this study, lisinopril was effective in controlling and reducing blood pressure in 71% of cases, and amlodipine was effective in 72% of cases. However, combination therapy with the same drug doses was effective in 100% of cases. The effectiveness of calcium channel blockers combined with ACE inhibitors, methyldopa, or beta blockers is enhanced.

In 90% of cases, mild to moderate hypertension is controlled with a combination of ACE inhibitors and calcium channel blockers, alpha-adrenergic blockers, or diuretics.

Isolated systolic hypertension is a strong risk factor for mortality and morbidity in cardiovascular diseases, including coronary artery diseases, stroke, and heart failure. Systolic hypertension increases the oxygen demand of the myocardium and can lead to acute coronary events. On the other hand, reducing systolic blood pressure in patients with ischemic heart disease can also be dangerous and should be considered. In this study, lowering blood pressure with combination therapy of amlodipine and lisinopril was effective. Additionally, in a double-blind placebo-controlled study, using 2 mg and 4 mg of the new calcium channel blocker lacidipine also significantly reduced and controlled systolic blood pressure.

Dihydropyridines like nifedipine cause acute diuresis and natriuresis, leading to the loss of sodium and water. The same effects have been shown with amlodipine. The loss of sodium and water activates the renin-angiotensin-aldosterone system, and after treatment with calcium channel antagonists, the concentration of angiotensin II increases. Adding ACE inhibitors blocks the activity of angiotensin II and enhances the effectiveness of calcium channel blockers in reducing blood pressure. Additionally, ACE inhibitors may enhance the activity of dihydropyridines by buffering baroreflex during the increase in heart rate due to vasodilation or indirectly by inhibiting the sympathetic system.

In this study, both amlodipine and lisinopril reduced blood pressure, but the combination of both drugs had a greater effect. Morgan and Anderson reported the excellent effectiveness of the combination of captopril and felodipine at lower doses in controlling and reducing blood pressure.

Short-acting dihydropyridines cause reflex tachycardia. In this study, monotherapy with amlodipine did not induce tachycardia, particularly in the standing position. Combining captopril with nifedipine prevents the tachycardia caused by nifedipine. In our study, no significant changes in heart rate were observed, suggesting no significant stimulation of the sympathetic system by amlodipine. Cappuccino and colleagues also reported similar results with 5 mg amlodipine.

One of the advantages of combination therapy is its greater impact on controlling hypertension and, on the other hand, reducing side effects. Our findings showed that the incidence of ankle edema and cough was much lower with combination therapy compared to monotherapy. Recently, a drug product containing amlodipine and bezapril was approved and launched in the market, showing high effectiveness in controlling hypertension with fewer side effects, especially ankle edema and headache, compared to monotherapy. In a dose-response relationship study involving 707 patients, enalapril and felodipine were used either as monotherapy or combination therapy, and it was observed that with combination therapy, the incidence of peripheral edema was significantly lower than with monotherapy with felodipine.

Combination therapy with ACE inhibitors and calcium channel blockers has other benefits as well. Reflex tachycardia caused by dihydropyridines is mitigated by the combination with ACE inhibitors, enhancing parasympathetic activity and reducing peripheral edema through the effects of post-capillary vasodilation induced by ACE inhibitors.

Many of the products on the market contain thiazide diuretics or beta blockers combined with calcium channel blockers. However, the present study demonstrated that combination therapy with calcium channel blockers and ACE inhibitors is more effective and has fewer side effects.

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