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Single-Arm Clinical Study of Combination Perindopril-Amlodipine Tablets in the Treatment of High-Altitude Hypertension

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Abstract: *Objective:* To evaluate the efficacy of combination perindopril/amlodipine tablets in patients with high-altitude hypertension who were previously unable to control their blood pressure with monotherapy. *Methods:* A total of 151 patients with high-altitude hypertension whose blood pressure remained inadequately controlled with previous monotherapy were enrolled in this study. All patients received an 8-week treatment with a combination of perindopril/amlodipine tablets, consisting of perindopril 10 mg/day and amlodipine 5 mg/day. Blood pressure measurements, including both diastolic and systolic pressures, were taken at baseline, and after 2, 4, 6, and 8 weeks of treatment. *Results:* After 8 weeks of treatment, there was a significant reduction in both average systolic and diastolic blood pressure compared to baseline ($P < 0.0001$). Specifically, the average systolic blood pressure decreased by 24.45 ± 13.75 mmHg, and the average diastolic blood pressure decreased by 13.37 ± 8.40 mmHg. The overall heart rate showed no significant changes during the treatment period. *Conclusion:* A combination of perindopril/amlodipine tablets significantly improved blood pressure control in patients with high-altitude hypertension after 8 weeks of treatment. These results support the efficacy of combination perindopril/amlodipine as a viable treatment option for high-altitude hypertension.

Keywords: High-altitude hypertension; Perindopril/amlodipine; Blood pressure control; Systolic and diastolic pressure reduction

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1. Introduction

High-altitude hypertension, also known as high-altitude pulmonary hypertension (HAPH), is a medical condition that affects individuals exposed to altitudes typically above 2,500 meters [1]. The reduced oxygen levels at these elevations can lead to various cardiovascular complications, including elevated blood pressure.

Upon entering high altitudes, the body undergoes acute stress responses to low oxygen levels, causing the sympathetic-adrenal system to become more active. This leads to an increase in biologically active substances, such as catecholamines, in the blood, which can promote elevated blood pressure. Consequently, cardiac output increases, vasoconstriction occurs in peripheral small blood vessels, and blood pressure rises. This process enhances blood perfusion to tissues and exhibits a certain degree of adaptive response. Over the course of several weeks to months, as adaptation occurs at the organ or cellular level, blood pressure gradually returns to normal [2-4]. However, in some individuals, dysregulation of the central nervous system's response to low oxygen levels results in sustained sympathetic activity, leading to widespread spasms of small arteries. Renal ischemia triggers renin secretion, further constricting small arteries, and creating a vicious cycle.

The treatment of high-altitude hypertension typically involves a combination of medication and lifestyle modifications [5-7]. Several medications are commonly used to manage this condition. Calcium channel blockers, such as amlodipine, are frequently prescribed to dilate blood vessels and reduce blood pressure. ACE inhibitors (e.g., perindopril) and angiotensin receptor blockers (ARBs) help relax blood vessels, easing the workload on the heart. Lifestyle modifications are also crucial, including lowering salt intake to reduce fluid retention, maintaining a healthy weight, regular exercise, and smoking cessation to help reduce blood pressure. Additionally, patients must take precautions to avoid altitude sickness. Gradual acclimatization, avoiding rapid ascent, and ensuring adequate rest and sleep can help alleviate symptoms of altitude sickness.

The combination of perindopril and amlodipine, known as perindopril/amlodipine, offers several advantages in treating high-altitude hypertension. The dual action of perindopril (an ACE inhibitor) and amlodipine (a calcium channel blocker) targets different pathways involved in blood pressure regulation, allowing for more effective and comprehensive control compared to monotherapy [8,9]. Amlodipine's calcium channel-blocking action induces vasodilation, counteracting the vasoconstrictive response often seen at high altitudes, where lower oxygen levels can elevate blood pressure. Furthermore, amlodipine's vasodilatory effects extend to coronary arteries, reducing the workload on the heart, which is particularly beneficial at high altitudes where cardiovascular demand increases. Perindopril's inhibition of the renin-angiotensin-aldosterone system (RAAS) further contributes to blood vessel relaxation and blood pressure reduction, particularly in response to altitude-related stress. Combining perindopril and amlodipine in a single-pill regimen simplifies treatment, potentially leading to improved patient adherence. The dual effects of perindopril/amlodipine may assist individuals in adapting to the physiological stresses associated with high altitudes, thereby minimizing the risk of altitude-related hypertension.

An observational study [10] conducted in a high-altitude region evaluated the antihypertensive efficacy of amlodipine in local hypertensive patients and found significantly elevated diastolic blood pressure in this population. Fifty-six resident Tibetan hypertensive patients (Tibetan group) and 50 Han hypertensive migrants (Han group) were treated with amlodipine 5 mg/day for 8 weeks. Both systolic and diastolic blood pressure significantly decreased after treatment. Systolic blood pressure dropped from 146.3 ± 3.4 mmHg/143.2 ± 4.1 mmHg to 132.7 ± 5.2 mmHg/128.4 ± 6.8 mmHg in the Tibetan and Han groups, respectively. However, the reduction in diastolic blood pressure was less pronounced, remaining at 93.3 ± 5.8 mmHg in the Han group, which did not reach the target level. Although amlodipine monotherapy exhibited good antihypertensive effects, its efficacy in reducing diastolic blood pressure was limited. Therefore, increasing the dosage or combining amlodipine with other antihypertensive drugs may be necessary to improve blood pressure control and requires further follow-up.

This study presents the results of a new combination strategy involving the single-pill perindopril/amlodipine fixed-dose combination as a second-line therapy. It evaluates its effectiveness in improving blood pressure control and protecting cardiovascular outcomes in patients with high-altitude hypertension. The dosage

of 5 mg amlodipine, specifically developed for this combination, is lower than the maximum registered dosage (equivalent to 10 mg/day in China).

2. Materials and methods

2.1. Study design and patients

This study was designed to evaluate the efficacy and safety of the perindopril/amlodipine combination in patients suffering from resistant high-altitude hypertension. Conducted at a research center in Lhasa, Tibet, this single-arm, open-label clinical trial included individuals diagnosed with this condition. Participants were required to be 18 years of age or older, with systolic blood pressure (SBP) between 140 and 180 mmHg, and diastolic blood pressure (DBP) between 95 and 110 mmHg. Patients who had been receiving up to two antihypertensive treatments were eligible, provided they were open to adjusting their medication regimen. However, those with secondary hypertension, recent cerebrovascular events, myocardial infarction, severe heart failure, significant valvular abnormalities, or other contraindications were excluded.

The study strictly followed the ethical guidelines outlined in the Declaration of Helsinki. Ethical approval was secured from the ethics committee or institutional review board of each participating center. Written informed consent was obtained from all participants before enrollment.

2.2. Evaluations

Throughout the study, patients attended several visits (baseline, 2, 4, 6, and 8 weeks), where supine blood pressure was measured using a validated automated device (OMRON model 705CP-II, cuff sizes: 22–32 cm or 32–42 cm). Blood pressure was taken three times consecutively on the same arm at 1-minute intervals, ensuring accuracy in compliance with regulatory standards. Patients rested for a minimum of 10 minutes before the first measurement, and the average of the last two readings was recorded. Investigators were thoroughly trained at the start of the trial to ensure consistency in procedures.

In addition to blood pressure, other assessments included vital signs, routine laboratory tests, physical examinations, and spontaneous reports of adverse events. If leg edema was reported, a clinical evaluation was conducted, and investigators documented the presence of visible leg edema at each study visit. The primary endpoint of the study was the change in systolic blood pressure (SBP) from baseline to 3 months (or the final post-baseline visit at 3 months). Secondary endpoints included changes in SBP and DBP at each study visit.

2.3. Statistical methods

The demographic data and baseline characteristics of the study population were summarized. The primary objective of the analysis was to assess the reductions in mean systolic blood pressure (msSBP) and mean diastolic blood pressure (msDBP) after 8 weeks of treatment compared to baseline.

To analyze the treatment effects, a linear mixed-effects model was applied, accounting for the interaction between treatment and study design, with an adjustment made for baseline systolic blood pressure. A significance level of $P < 0.05$ was set for the analysis. However, as this was a single-arm study without pre-study statistical assumptions, only descriptive summaries were provided.

For the Full Analysis Set, missing values for the primary efficacy endpoint (blood pressure) were imputed using the Last Observation Carried Forward (LOCF) method, utilizing the closest available observation. No imputation was performed for other missing variables. All statistical analyses were conducted using the SAS

Statistical Package Version 9.2.

3. Results

A total of 153 patients were screened for the study, and 151 were enrolled and received treatment. Of these, 132 participants completed the 8-week study. The primary reasons for early withdrawal included loss to follow-up (n = 6) and withdrawal of informed consent (n = 4).

The average treatment duration with perindopril/amlodipine tablets was 53 ± 9 days (full analysis set population). Adherence to the study treatment was high. Before medication, patients had baseline diastolic and systolic blood pressures of 100.15 ± 4.15 mmHg and 158.30 ± 7.27 mmHg, respectively (**Table 1**). With perindopril/amlodipine treatment, seated blood pressure gradually decreased. By the 8th week, the average diastolic blood pressure was 86.77 ± 9.21 mmHg, representing a reduction of 13.37 ± 8.40 mmHg compared to baseline. Similarly, the average systolic blood pressure in the 8th week was 133.85 ± 14.02 mmHg, reflecting a reduction of 24.45 ± 13.75 mmHg compared to baseline. Using a two-factor analysis of variance and intra-group comparison tests, both diastolic and systolic blood pressures showed clinically significant reductions after treatment ($P < 0.0001$, **Table 2**).

Table 1. Patient's blood pressure after medication use

		n	**SD**
Systolic blood pressure	Before treatment	151	158.30 ± 7.27
	2 weeks	151	137.37 ± 14.11
	4 weeks	151	136.17 ± 15.73
	6 weeks	151	133.23 ± 14.65
	8 weeks	151	133.85 ± 14.02
Diastolic blood pressure	Before treatment	151	100.14 ± 4.15
	2 weeks	151	87.87 ± 8.82
	4 weeks	151	87.56 ± 9.99
	6 weeks	151	85.91 ± 9.69
	8 weeks	151	86.77 ± 9.21

Table 2. Patients' changes in blood pressure compared to the baseline

		n	**Mean ± SD**	**95% CI**	***t***	***P***
Systolic blood pressure	2 weeks	151	-20.93 ± 12.60	(-22.96, -18.91)	20.42	< 0.0001
	4 weeks	151	-22.14 ± 14.12	(-24.41, -19.87)	19.26	< 0.0001
	6 weeks	151	-25.07 ± 13.73	(-27.28, -22.87)	22.44	< 0.0001
	8 weeks	151	-24.45 ± 13.75	(-26.66, -22.24)	21.85	< 0.0001
Diastolic blood pressure	2 weeks	151	-12.26 ± 7.87	(-13.53, -11.00)	19.15	< 0.0001
	4 weeks	151	-12.58 ± 8.74	(-13.99, -11.18)	17.68	< 0.0001
	6 weeks	151	-14.23 ± 8.41	(-15.58, -12.88)	20.79	< 0.0001
	8 weeks	151	-13.37 ± 8.40	(-14.72, -12.02)	19.55	< 0.0001

During the study, a total of 98 subjects experienced adverse events, corresponding to an incidence rate of 64.90%. Adverse events with an incidence of ≥ 1% during treatment with perindopril/amlodipine included: elevated triglycerides, increased uric acid, elevated cholesterol, elevated blood glucose, increased creatine kinase, elevated low-density lipoprotein, proteinuria, elevated alanine aminotransferase, positive leukocytes in urine, hematuria, elevated aspartate aminotransferase, upper respiratory tract infection, urinary tract infection, dizziness, headache, and hyperlipidemia. Perindopril/amlodipine tablets demonstrated good safety, with no new adverse events reported beyond those previously associated with the individual medications, consistent with findings from prior studies.

4. Discussion

The fixed-dose combination of perindopril/amlodipine, with an initial dose of 10/5 mg, demonstrated effective blood pressure reduction in high-altitude hypertensive patients for whom single-drug therapy was insufficient. This reduction became apparent within the first 2 weeks of treatment and remained statistically significant throughout the entire treatment period. The combination of perindopril and amlodipine showed similar effectiveness in terms of absolute reductions in systolic and diastolic blood pressure ($P \leq 0.001$ at each visit).

Disclosure statement

The authors declare no conflict of interest.

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