

ORIGINAL ARTICLE

Ambulatory blood pressure response to S-amlodipine in Korean adult patients with uncontrolled essential hypertension: A prospective, observational study

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Abstract

Although amlodipine is recommended as the first-line therapy for the treatment of hypertension, its use is limited by its potential side effects. S-amlodipine is expected to be able to minimize side effects of amlodipine with a similar antihypertensive effect by removing the malicious R-chiral form. However, sustainable blood pressure control with S-amlodipine has not been well established yet. The purpose of the current study was to evaluate ambulatory blood pressure (ABP) profiles before and after a 12-week treatment of S-amlodipine. Patients received once-daily S-amlodipine 2.5 or 5 mg. ABP during 24 hr and office blood pressure were measured at baseline and after the 12-week treatment. Primary endpoints were changes of systolic and diastolic 24 hr ABP. After 12-week S-amlodipine treatment, mean systolic ABP (-15.1 ± 16.2 mmHg, $p < .001$) and diastolic ABP (-8.9 ± 9.8 mmHg, $p < .001$) were decreased significantly. Both daytime and night-time mean systolic BP and diastolic BP were also significantly decreased after the 12-week treatment. Global trough-to-peak ratio and smoothness index after 12-week S-amlodipine treatment were .75 and .79 for SBP and .65 and .61

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for DBP, respectively. Age ≥ 65 years (hazard ratio [HR]: 3.13; 95% confidence interval [CI]: 1.67–14.3) and nonalcohol drinking (HR: 3.09; 95% CI: 1.34–7.17) were independent clinical factors for target ABP achievement. Adverse drug reactions (ADR) were developed in 16 (6.4%) patients, including two (.8%) cases of peripheral edema. In conclusion, this study demonstrated the efficacy and safety of S-amlodipine in patients with uncontrolled essential hypertension.

KEYWORDS

ambulatory, blood pressure monitoring, chirality, essential hypertension, S-amlodipine, safety

1 | INTRODUCTION

Calcium channel blocker (CCB) is recommended as the first-line antihypertensive drug in the current hypertension management guidelines.¹ CCB can inhibit voltage-dependent L-type calcium channels in vascular smooth muscle cells. Consequently, the amount of Ca^{2+} entering into vascular smooth muscle cells diminishes, which causes vascular smooth muscle to dilate and subsequently decreases the peripheral resistance. CCB has a broad spectrum of indications for treating hypertension, including patients with combined diabetes mellitus, chronic kidney disease, ischemic heart disease, and heart failure.² Among subclasses of CCB, dihydropyridine CCB is preferred to nondihydropyridine CCB in patients with ischemic heart disease and heart failure with reduced ejection fraction because of its efficacy and safety.³

In pharmacokinetic analyses of dihydropyridine CCB, amlodipine demonstrated the best oral bioavailability and the longest half-life. Such properties enabled amlodipine to maintain consistent control of blood pressure (BP).⁴ Nonetheless, unintended adverse events (AE) including peripheral edema limited the use of amlodipine. Conventional amlodipine has a chirality composed of (R-) and (S-) amlodipine isomers at a 1:1 ratio. Only S-amlodipine is known as the active isomer with therapeutic effects.⁵ Therefore, using S-amlodipine isolated from conventional amlodipine is expected to lessen AE with similar efficacy. Comparison between amlodipine and S-amlodipine has demonstrated a reduced risk of peripheral edema with the use of S-amlodipine.^{4–7}

Nevertheless, consistency and magnitude of BP reduction throughout 24-hr with S-amlodipine have not been well understood. Therefore, the objective of the present study was to evaluate the efficacy for 24 hrs with ambulatory BP (24 hr ambulatory blood pressure [ABP]) and safety of S-amlodipine in uncontrolled essential hypertension patients.

2 | METHODS

2.1 | Study population and protocol

A total of 338 patients with uncontrolled essential hypertension were selected from cardiovascular clinics of 10 tertiary hospitals in South Korea. Inclusion criteria were as follows: ≥ 18 years old, use of antihy-

pertensive medication (angiotensin-converting class enzyme inhibitor, angiotensin receptor blocker, nondihydropyridine CCB, beta-blocker, alpha-blocker, and diuretics), more than two times of outpatient clinic visits with BP $\geq 140/90$ mmHg during the previous 12 months, and mean BP $\geq 140/90$ mmHg during the previous 6 months. Exclusion criteria were: patients with dihydropyridine medication, previous history of AE with dihydropyridine, mean systolic BP ≥ 200 mmHg, secondary hypertension, pregnancy or breastfeeding, severe aortic stenosis, severe hepatic dysfunction, or myocardial infarction within one month. The study protocol included the following. At the initial visit (visit 1), all selected patients received physical examinations, including measuring of their office BP. Their medical histories were reviewed to sort candidates meeting the inclusion and exclusion criteria. After screening, patients who met the inclusion and exclusion criteria were advised to revisit within one week and S-amlodipine 2.5 or 5 mg once daily was added to their conventional antihypertension medication (visit 2). Office BP and 24 hr ABP were measured at the second visit (baseline) and the 12-week follow-up visit (visit 3) with the same device at each measurement. All AE were recorded at every visit (Figure 1). There were no changes to other antihypertensive medications during the study period. Patients had good drug adherence to S-amlodipine. All participants provided informed consent. This study was conducted in accordance with the guidelines of The Declaration of Helsinki. This study was approved by the ethics committee of Chonnam National University Hospital, Gwangju, South Korea (approval number: CNUH-2017-178).

2.2 | Study definition

Office BP was defined as the average BP of three measurements taken two minutes apart. Before taking BP measurement, enrolled patients refrained from smoking and drinking any caffeinated beverage for 1 hr and stayed seated for more than 5 min. To obtain 24 hr ABP, BP was measured with 30-min intervals during daytime and 1 hr intervals at nighttime for 24 hrs. The median daytime blood pressure was defined as the average of systolic and diastolic ABP measured from 7 a.m. to 10 p.m. The median night blood pressure was defined as the average of systolic and diastolic ABP measured from 10 p.m. to 6 a.m. Target 24 hr ABP was defined as 24 hr SBP/DBP $< 130/80$ mmHg. The 24 hr

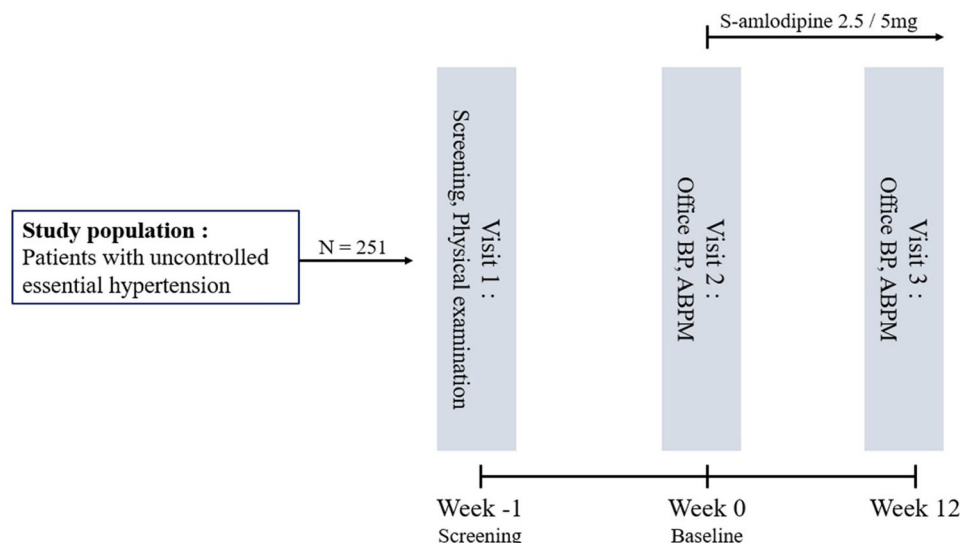


FIGURE 1 Study population and protocol. BP, blood pressure; ABPM, ambulatory blood pressure measurement

distribution of BP reduction was evaluated based on trough-to-peak (T/P) ratio and smoothness index (SI). T/P ratio was defined as the ratio of the change in ABP in the last 2 hrs (22–24 hrs postadministration, 2 hrs before next dosing) after taking S-amlodipine (trough) divided by the maximum fall in BP that was maintained for 1 hr from the baseline (peak).⁸ SI was calculated by dividing the mean ABP fluctuation from every hour by the standard deviation (SD) of hourly changes during the total 24 hr period.⁹

The primary efficacy endpoint was the change in 24 hr ABP after administration of S-amlodipine for 12 weeks. Secondary efficacy endpoints were changes in median systolic and diastolic ABP during daytime and night, changes in office BP, T/P ratio, and SI. Safety endpoints were divided into AE and adverse drug reactions (ADR). AE was defined as all harmful and unintended signs and symptoms or diseases that occurred in subjects receiving S-amlodipine. ADR was defined as any AEs that might be related to S-amlodipine. The intensity of AE/ADRs was classified as mild (i.e., mild symptoms or signs that did not affect daily activities), moderate (i.e., slight limitations in daily activities), or severe (i.e., marked limitations in daily activities).

2.3 | Statistical analysis

BP measurements from baseline to week 12 were analyzed by paired *t*-test. Continuous variables are presented as means \pm standard deviations. They were compared with unpaired Student's *t*-tests or Mann-Whitney *U*-tests. Discrete variables are expressed as percentages and frequencies. They were compared using chi-square statistics or Fisher's exact test. Subgroup analysis for change of 24 hr BP was analyzed by paired *t*-test between gender and age groups. The difference between subgroups was determined by interaction *p*-values. T/P ratio and SI were evaluated with the Kruskal-Wallis test. Multivariate logistic regression analysis was used to determine factors that influenced the achievement of target ABP level. Odds ratio (OR) and

95% confidence interval (CI) were obtained. All analyses were conducted using Stata version 13.1 (StataCorp, College Station, Texas, USA). Statistical significance was defined when *p*-value was less than .05 ($p < .05$).

3 | RESULTS

3.1 | Study population

A total of 338 patients satisfied the inclusion criteria and exclusion criteria. Of them, 87 were excluded (13 patients were excluded due to withdrawal of consent participation of the study, 31 patients were excluded due to violation of the clinical trial protocol, 25 patients were excluded due to follow-up loss). Finally, 251 patients were enrolled in the study. In the total study population, the mean age was 54.7 ± 14.4 years old. There were 153 (60.9%) male patients and 82 (32.7%) current smokers. As for previous antihypertensive medication, 203 (80.9%) patients were taking angiotensin receptor blockers, 25 (9.9%) were having beta-blockers, and 34 (13.5%) were taking combination drugs. Regarding other medical conditions, 41 (16.3%) patients had a medical history of dyslipidemia, 25 (9.9%) had diabetes, 14 (5.6%) had heart failure, and 8 (3.2%) had cerebrovascular disease (Table 1).

3.2 | Impact of S-amlodipine on 24 hr ABP

The mean and change of 24 hr ABP at baseline and after 12 weeks of treatment with S-amlodipine are presented in Figure 2. Both 24 hr systolic ABP (140.05 ± 15.67 mmHg vs. 124.94 ± 12.95 mmHg, -15.10 ± 16.22 mmHg, $p < .0001$) and diastolic ABP (87.83 ± 11.58 mmHg vs. 78.94 ± 9.28 mmHg, -8.85 ± 9.82 , $p < .0001$) were markedly decreased. The median daytime ABP was significantly decreased for both systolic ABP (147.55 ± 14.47 mmHg vs.

TABLE 1 Study populations

	Total (n = 251)
Sex, n (%)	
Male	153 (60.9)
Female	98 (39.1)
Age, years	54.7 ± 14.4
Age ≥65 years, n (%)	68 (27.1)
S-amlodipine 5 mg, n (%)	36 (14.3)
Smoking, n (%)	
Non-smoker	169 (67.3)
Current smoker	82 (32.7)
Alcohol drinking, n (%)	
Yes	68 (27.1)
No	183 (72.9)
Comorbidity, n (%)	
Myocardial infarction	6 (2.4)
Heart failure	14 (5.6)
Peripheral artery disease	4 (1.6)
Diabetes	25 (9.9)
Chronic kidney disease	5 (1.9)
Dyslipidemia	41 (16.3)
Cerebrovascular disease	8 (3.2)
Previous antihypertensive drugs, n (%)	
Non-dihydropyridine calcium channel blocker	5 (1.9)
β-blocker	25 (9.9)
Diuretics	4 (1.6)
Angiotensin converting enzyme inhibitor	13 (5.2)
Angiotensin receptor blocker	203 (80.9)
α-blocker	1 (.4)
Combination	34 (13.5)

Note: Values are presented as the n (%) of patients or mean ± SD.

132.12 ± 13.52 mmHg, −15.54 ± 15.80 mmHg, $p < .0001$) and diastolic ABP (93.52 ± 11.86 mmHg vs. 83.91 ± 10.39 mmHg, −9.64 ± 9.10 mmHg, $p < .0001$). Likewise, the mean nighttime ABP showed significant reduction for both systolic ABP (136.30 ± 17.58 mmHg vs. 121.36 ± 13.94 mmHg, −14.88 ± 17.82 mmHg, $p < .0001$) and diastolic ABP (84.99 ± 12.29 mmHg vs. 76.45 ± 9.58 mmHg, −8.46 ± 11.13 mmHg, $p < .0001$) (Table 2, Figure 3).

3.3 | Impact of S-amlodipine on office blood pressure

The average office BP was 154.23 ± 15.41/93.89 ± 14.07 mmHg at baseline and 132.63 ± 15.63/80.53 ± 11.93 mmHg at 12 weeks after administration of S-amlodipine. Mean office SBP and DBP at 12 weeks were significantly decreased (−21.60 ± 18.08 mmHg and

13.36 ± 13.35 mmHg, respectively, both $p < .0001$) compared to those at baseline (Table 2, Figure 3).

3.4 | Effect of S-amlodipine on 24 hr BP control

After 12 weeks of administration of S-amlodipine, both mean systolic and diastolic blood pressure were significantly decreased at the last 2 hr period of monitoring (22–24 hrs postadministration) compared to those before treatment, which resulted in a high T/P ratio. The global T/P ratio of the mean ABP after administration of S-amlodipine was .75 for SBP and .65 for DBP. The distribution of BP after administration of S-amlodipine showed little changes in both systolic and diastolic BP compared to that at baseline. The SI was .79 for SBP and .61 for DBP SI.

3.5 | Safety endpoint of S-amlodipine

During the study period, 20 (7.9%) patients reported AE and 16 (6.4%) patients had ADR. Majority of these AE and ADR were mild or moderate. Peripheral edema was detected in 2 (.8%) patients. Total incidence of AE and ADR is summarized in Table 3.

3.6 | Subgroup analysis

The efficacy of S-amlodipine was compared among subgroups. Both male and female subgroups showed decreased 24 hr systolic ABP (−13.76 ± 17.13 mmHg vs. −17.00 ± 14.76 mmHg, interaction $p = .203$) and diastolic ABP (−9.01 ± 9.88 mmHg vs. −8.63 ± 9.81 mmHg, interaction $p = .616$) after 12 weeks of administering S-amlodipine compared to baseline values. Both ≥65 years and <65 years subgroups showed decreased 24 hr systolic ABP (−16.45 ± 15.57 mmHg vs. −14.58 ± 16.51 mmHg, interaction $p = .521$) and diastolic ABP (−8.22 ± 9.11 mmHg vs. −9.10 ± 10.12 mmHg, interaction $p = .625$) after 12 weeks of administering S-amlodipine compared to their respective baseline values.

3.7 | Independent clinical parameter for successful target range of ABP

A total of 129 (51.3%) patients successfully achieved therapeutic target ABP. Multivariate logistic regression analysis showed that age ≥65 years (hazard ratio [HR]: 3.13; 95% CI: 1.67–14.3; $p = .012$) and having a nonalcohol drinking behavior (HR: 3.09; 95% CI: 1.34–7.17; $p = .008$) were independent clinical parameters for successful target ABP achievement (Table 4).

4 | DISCUSSION

This study had the following principal findings: (i) treatment with S-amlodipine for 12 weeks significantly decreased both systolic and diastolic 24 hr ABP in uncontrolled essential hypertension patients already under other antihypertensive medication compared to baseline, with

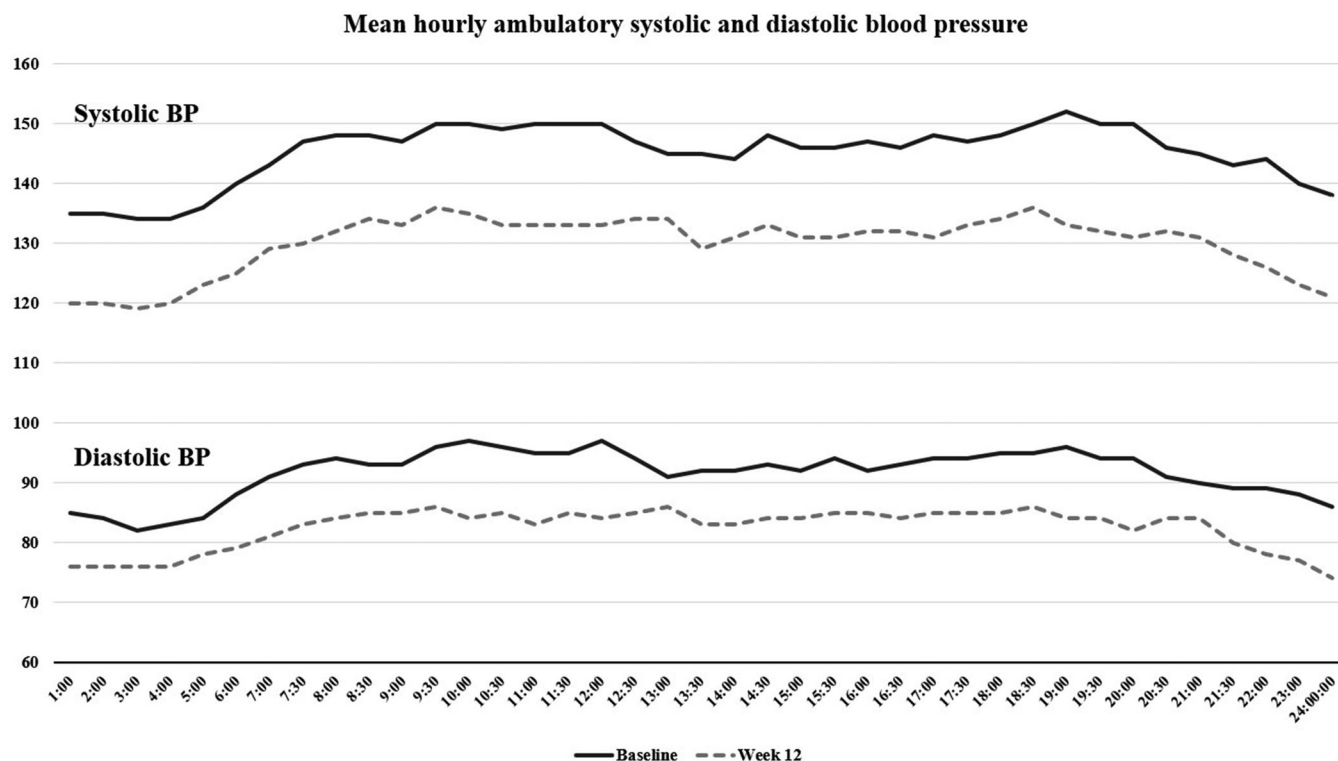


FIGURE 2 Mean hourly ambulatory systolic and diastolic blood pressure profiles at baseline and after 12-week treatment of S-amlodipine. BP, blood pressure

TABLE 2 Changes of 24 hr ABP and office BP with S-amlodipine

	Baseline	Week 12	Change	p-Value
24 hr ABP				
SBP, mmHg	140.05 ± 15.67	124.94 ± 12.95	-15.10 ± 16.22	<.0001
DBP, mmHg	87.83 ± 11.58	78.94 ± 9.28	-8.85 ± 9.82	<.0001
Daytime mean BP				
SBP, mmHg	147.55 ± 14.47	132.12 ± 13.52	-15.54 ± 15.80	<.0001
DBP, mmHg	93.52 ± 11.86	83.91 ± 10.39	-9.64 ± 9.10	<.0001
Nighttime mean BP				
SBP, mmHg	136.30 ± 17.58	121.36 ± 13.94	-14.88 ± 17.82	<.0001
DBP, mmHg	84.99 ± 12.29	76.45 ± 9.58	-8.46 ± 11.13	<.0001
Office BP				
SBP, mmHg	154.23 ± 15.41	132.63 ± 15.63	-21.60 ± 18.08	<.0001
DBP, mmHg	93.89 ± 14.07	80.53 ± 11.93	-13.36 ± 13.35	<.0001

Note: Values are presented as the mean ± SD.

Abbreviations: ABP, ambulatory blood pressure; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

51.3% of patients from the total study population successfully reaching their therapeutic target ABP levels; and (ii) age ≥ 65 years and nonalcohol drinking behavior were independent clinical parameters for achieving successful target ABP. This is the first study that evaluates the efficacy of S-amlodipine through 24 hrs of ABP monitoring. The T/P ratio after treatment with S-amlodipine was .75 for systolic BP and .67 for diastolic BP, consistent with the action duration of S-amlodipine upon administration. This study also revealed that S-amlodipine was well tol-

erated by the study population. Only mild or moderate AE and ADR were noted in 5 (2.0%) and 3 (1.2%) patients, respectively.

Amlodipine is one of the most commonly used third-generation dihydropyridine CCB. It is mainly prescribed for the treatment and management of hypertension and angina. Conventional amlodipine is a racemic 1:1 mixture of (S-) and (R-) enantiomers.^{4,5} One enantiomer of a racemic drug retains the effect of the desired pharmacologic process, while the other enantiomer may either be inactive or have

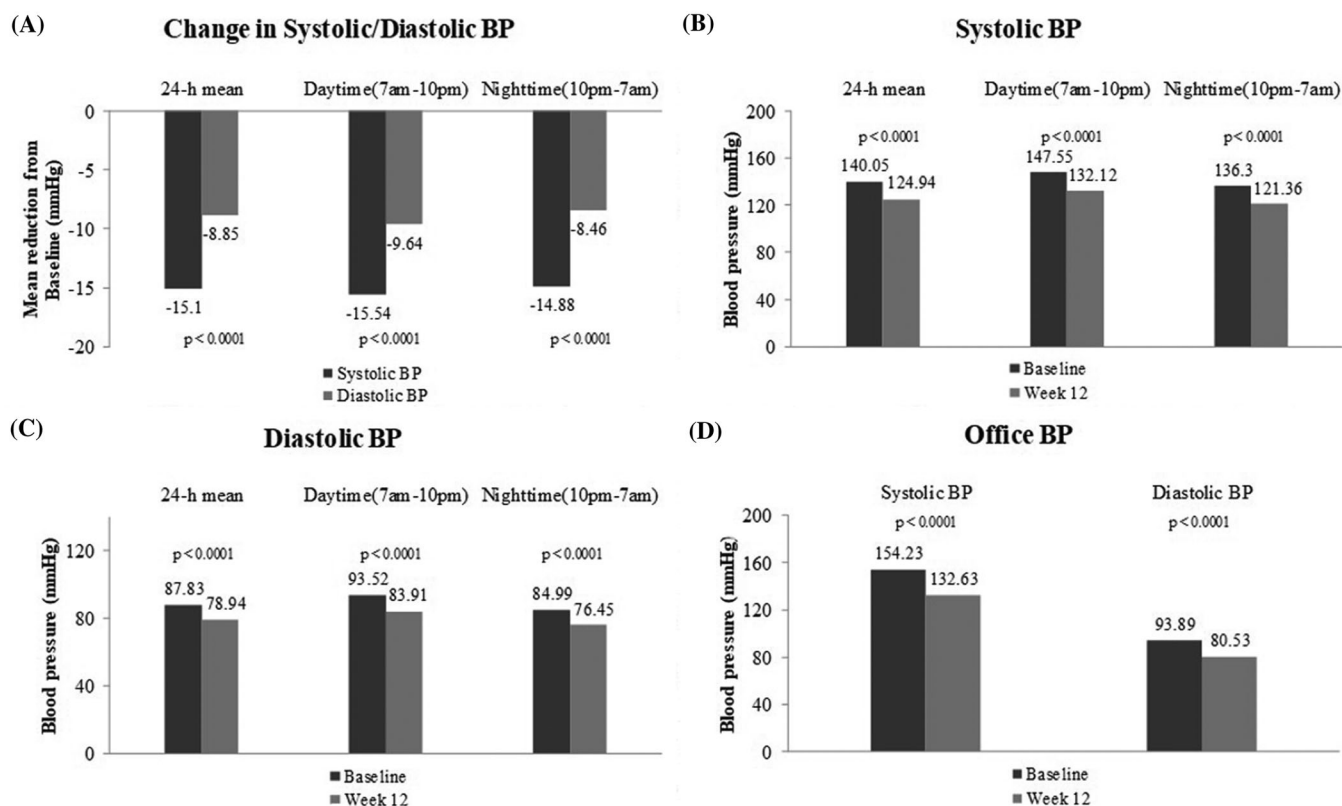


FIGURE 3 Effects of S-amlodipine. (A) Mean systolic and diastolic blood pressure reduction. (B) Systolic blood pressure. (C) Diastolic blood pressure. (D) Office blood pressure. BP, blood pressure

variable activity. Separating these enantiomers can result in better pharmacokinetics with fewer side effects.⁶ Previous studies have demonstrated that S-amlodipine has a strong affinity for L-type calcium ion channels, coupled with an antihypertensive effect 1,000 times greater than that of R-amlodipine. On the other hand, R-amlodipine has minimal antihypertensive effects.^{3,5,7} It is associated with side effects such as peripheral edema and facial flushing.⁷ Over the last two decades, S-amlodipine has been used worldwide since its approval in China in 1999.¹⁰⁻¹²

Many previous studies have demonstrated the clinical efficacy and safety of S-amlodipine for the treatment of hypertension. Previous studies have also compared the efficacy and safety of S-amlodipine with conventional amlodipine.¹³⁻¹⁶ Sen and colleagues have evaluated the efficacy of S-amlodipine 2.5 and 5 mg for 19 patients who were treatment-naïve and 14 patients who were previously treated by other antihypertensive medications (monotherapy). After 8 weeks of treatment, systolic 24 hr ABP was markedly decreased in both treatment-naïve (-15.3 ± 7.6 mmHg, $p < .0001$) and antihypertensive medication groups (-7.6 ± 5.5 mmHg, $p = .05$). After 8 weeks of treatment, diastolic 24 hr ABP was also markedly decreased in both treatment-naïve (-9.4 ± 5.1 mmHg, $p < .0001$) and antihypertensive medication groups (-4.8 ± 6.5 mmHg, $p = .043$).¹⁵ Meanwhile, Kim and colleagues have compared the efficacy of S-amlodipine 2.5 mg ($n = 63$) and conventional amlodipine 5 mg ($n = 61$) among 124 patients diagnosed as mild to moderate hypertension (defined as 90 mm Hg \leq diastolic blood pres-

sure ≤ 109 mm Hg). After 8 weeks of treatment, both treatment groups showed statistically similar reductions of sitting SBP (S-amlodipine -17.6 ± 11.2 mmHg vs. conventional amlodipine -18.6 ± 12.3 mmHg) and DBP (S-amlodipine -12.5 ± 6.7 mmHg vs. conventional amlodipine -12.5 ± 7.1 mmHg).¹⁶ The present study distinctively demonstrated the efficacy of S-amlodipine among patients who were considered as uncontrolled essential hypertension despite their treatments with other antihypertensive medications (mainly with angiotensin receptor blockers, 80.9%). After 12 weeks of administering S-amlodipine, systolic 24 hr ABP (-15.10 ± 16.22 mmHg), diastolic 24 hr ABP (-8.85 ± 9.82 mmHg), and office BP (systolic: -21.60 ± 18.08 mmHg, diastolic: -13.36 ± 13.35 mmHg) were all significantly decreased. Among adverse effects or ADR of CCB, peripheral edema, especially in the lower extremities, was common. Reported rates of peripheral edema ranged from 10% to 70%.⁷ Theoretically, S-amlodipine poses a lower risk for the development of peripheral edema than conventional amlodipine.¹⁷ Although there are some conflicting results, a previous randomized trial comparing the incidence of peripheral edema among patients under either S-amlodipine or conventional amlodipine by Galappathy and colleagues showed that S-amlodipine reduced the incidence and risk of peripheral edema.^{17,18} In the current study, only 2 (.8%) patients suffered from peripheral edema and only 1 (.4%) patient showed moderate AE and moderate ADR. The incidence of peripheral edema was relatively low in the current study compared to those in other previous studies.^{16,18} Nevertheless, the current real-world data

TABLE 3 Safety endpoints with S-amlodipine

	AE (ADR)	Total (n = 251)
General, n (%)	5 (4)	5 (2.0)
Myalgia	2 (1)	2 (.8)
Peripheral edema	2 (2)	2 (.8)
Leg pain	1 (1)	1 (.4)
Cardiopulmonary, n (%)	7 (5)	7 (2.8)
Chest pain	3 (2)	3 (1.2)
Palpitation	2 (1)	2 (.4)
Dyspnea	1 (1)	1 (.4)
Orthostatic hypotension	1 (1)	1 (.4)
Gastro-intestinal, n (%)	5 (4)	5 (2.0)
Constipation	1 (0)	1 (.4)
Abdominal pain	1 (1)	1 (.4)
Dyspepsia	2 (2)	2 (.8)
Anorexia	1 (1)	1 (.4)
Nervous system n (%)	6 (5)	6 (2.4)
Dizziness	2 (2)	2 (.8)
Decreased sense	1 (1)	1 (.4)
Headache	1 (1)	1 (.4)
Gait disturbance	1 (1)	1 (.4)
Sleep disturbance	1 (0)	1 (.4)
Urologic system n (%)	1 (1)	1 (.4)
Hematuria	1 (1)	1 (.4)
AE		
Total event/patient, n (%)	24	20 (7.9)
ADR		
Total event/patient, n (%)	19	16 (6.4)
Moderate AE, n (%)	5	5 (2.0)
Peripheral edema	1	1 (.4)
Chest pain	1	1 (.4)
Palpitation	1	1 (.4)
Dyspnea	1	1 (.4)
Gait disturbance	1	1 (.4)
Moderate ADR, n (%)	3	3 (1.2)
Peripheral edema	1	1 (.4)
Dyspnea	1	1 (.4)
Gait disturbance	1	1 (.4)

Note: Values are presented as the n (%) of patients.

Abbreviations: AE, adverse effect; ADR, adverse drug reaction.

could support peripheral edema safety outcomes of S-amlodipine. Total incidence of AE (7.9%) and ADR (6.4%) were also lower than those reported by Kim and colleagues¹⁶

The T/P ratio is a value that measures the distribution of BP reductions over 24 hrs afforded by a given antihypertensive drug in question. It indicates the therapeutic duration of the medication. A high T/P ratio with a value close to 1.0 indicates that the therapeutic duration of the

TABLE 4 Independent clinical factors for successful target ABP range achievement

Successful therapeutic target ABP range, n (%)	129 (51.3)	
Clinical parameters	OR (95% CI)	p-Value
Male	2.46 (.98–6.16)	.054
Age ≥65 years	3.13 (1.67–14.3)	.012
Smoking	.61 (.87–2.14)	.089
Non-alcohol drinking	3.09 (1.34–7.17)	.008
Heart failure	1.07 (.27–4.23)	.921
Diabetes	.67 (.20–2.17)	.495
Dyslipidemia	.60 (.19–1.93)	.389

Abbreviations: ABP, ambulatory blood pressure; OR, odds ratio; CI, confidence interval.

antihypertensive medication is long enough to provide optimal therapeutic coverage for 24 hrs.¹⁹ Meanwhile, the SI is a value that measures both the consistency and magnitude of BP reduction by a given drug throughout 24 hrs. A high SI with a value >1 is most desirable, indicating a large and consistent BP reduction. The SI has been shown as an independent predictor of treatment-induced reductions in target-organ damage.^{20,21} A previous study has revealed that the global T/P ratio after 12-week treatment of conventional 5 mg amlodipine is .56 for SBP and .56 for DBP.²² To the best of our knowledge, the present study is the first one assessing the T/P ratio and the SI of S-amlodipine through 24 hrs. The calculated global T/P ratio after administration of S-amlodipine in the present study was .75 for SBP and .65 for DBP, indicating that the therapeutic duration of S-amlodipine was sufficient and comparable to conventional amlodipine. The calculated SI after administration of S-amlodipine was .79 for SBP and .61 for DBP.

The present study has several limitations. First, the current study did not compare the efficacy or safety between S-amlodipine and conventional amlodipine. The advantage of S-amlodipine might have been prominent if it was compared to conventional amlodipine. Although most patients in the study population were previously being treated with angiotensin receptor blockers, precise information of the drug and its dosage is lacking. Additionally, other antihypertensive medications instead of an angiotensin receptor blocker were used in the remaining 20% of the study population. Therefore, efficacy and safety outcomes might be related to other hypertensive medications. Second, the current study lacked further information about the distribution of 2.5 and 5 mg S-amlodipine. Differences in dosages of S-amlodipine might have an impact on 24 hr ABP and office BP reduction. Third, information about BP variability was limited in the present study. Although the current study was the first study to estimate 24 hr distribution of BP reduction of S-amlodipine in uncontrolled hypertension patients, interval changes of T/P ratio, SI before and after treatment of S-amlodipine, average real variability index, and chaotic variation might be more precise parameters for 24 hr BP variability of S-amlodipine. Therefore, for results to be generalized to all patients with hypertension, the efficacy and safety of S-amlodipine should be confirmed in more compelling and definitive controlled multicenter, long-term follow-up studies.

5 | CONCLUSIONS

Twelve weeks of S-amlodipine treatment significantly reduced 24 hr ABP and office BP compared to those at baseline in selected patients with uncontrolled essential hypertension. S-amlodipine was well tolerated. The incidence of peripheral edema was only .8% in the current study population. The therapeutic duration of S-amlodipine was sufficient and comparable to conventional amlodipine. Age and alcohol drinking history were significantly associated with the achievement of target range ABP.

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CONFLICTS OF INTEREST

The authors have no potential conflicts of interest relevant to this study to disclose.

AUTHORS CONTRIBUTION

KHL contributed to conceptualization, project administration, study design, data management and validation. DKK and JHA were responsible for, data interpretation and manuscript preparation. SHK, SSK, JON responsible for data collection and data management. SDP, KTA and JHL were responsible for data collection, data interpretation. JKS and WGC were responsible for data collection and manuscript preparation. All authors read and approved the final manuscript.

REFERENCES

- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014; 311:507-520.
- Katz AM. Pharmacology and mechanisms of action of calcium-channel blockers. *J Clin Hypertens*. 1986; 2:28S-37S.
- Sica DA. Pharmacotherapy review: calcium channel blockers. *J Clin Hypertens*. 2006; 8:53-56.
- Levine CB, Fahrback KR, Frame D, et al. Effect of amlodipine on systolic blood pressure. *Clin Ther*. 2003; 25:35-57.
- Sheraz MA, Ahsan SF, Khan MF, Ahmed S, Ahmad I. Formulations of amlodipine: a review. *J Pharm*. 2016; 2016:8961621.
- Patil PA, Kotheekar MA. Development of safer molecules through chirality. *Indian J Med Sci*. 2006; 60:427-437.
- M Makani H, Bangalore S, Romero J, et al. Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate—a meta-analysis of randomized trials. *J Hypertens*. 2011; 29:1270-1280.
- Diamant M, Vincent HH. Lisinopril versus enalapril: evaluation of trough: peak ratio by ambulatory blood pressure monitoring. *J Hum Hypertens*. 1999; 13:405-412.
- Coca A, Sobrino J, Soler J, et al. Trough-to-peak ratio, smoothness index, and circadian blood pressure profile after treatment with a once-daily fixed combination of losartan 100 and hydrochlorothiazide 25 in essential hypertension. *J Cardiovasc Pharmacol*. 2002; 39:824-833.
- Dalal J, Mohan JC, Iyengar SS, et al. S-Amlodipine: an isomer with difference-time to shift from racemic amlodipine. *Int J Hypertens*. 2018; 2918:8681792.
- Liu F, Qiu M, Zhai SD. Tolerability and effectiveness of (S)-amlodipine compared with racemic amlodipine in hypertension: a systematic review and meta-analysis. *Curr Ther Res Clin Exp*. 2010; 71:1-29.
- Gyu-Chul Oh, Hae-Young Lee, Hyun-Jae Kang, Joo-Hee Zo, Dong-Ju Choi, Byung-Hee Oh. Quantification of pedal edema during treatment with S(-)-amlodipine nicotinate versus amlodipine besylate in female Korean patients with mild to moderate hypertension: a 12-week, multicenter, randomized, double-blind, active-controlled, phase IV clinical trial. *Clin Ther*. 2012; 34:1940-1947.
- Pathak L, Hiremath Kerkar PG, Manade VG. Multicentric clinical trial of S-amlodipine 2.5 mg versus amlodipine 5 mg in the treatment of mild to moderate hypertension—a randomized, double-blind clinical trial. *J Assoc Physicians India*. 2004; 52:197-202.
- Chen Q, Huang QF, Kang YY, et al. Efficacy and tolerability of initial high vs low doses of S(-)-amlodipine in hypertension. *J Clin Hypertens*. 2017; 19:973-982.
- Şen S, Demir M, Yiğit Z, Üresin AY. Efficacy and safety of S-amlodipine 2.5 and 5 mg/d in hypertensive patients who were treatment-naive or previously received antihypertensive monotherapy. *J Cardiovasc Pharmacol Ther*. 2018; 23:318-328.
- Kim SA, Park S, Chung N, et al. Efficacy and safety profiles of a new S(-)-amlodipine nicotinate formulation versus racemic amlodipine besylate in adult Korean patients with mild to moderate hypertension: an 8-week, multicenter, randomized, double-blind, double-dummy, parallel-group, phase III, noninferiority clinical trial. *Clin Ther*. 2008; 30:845-857.
- Pedrinelli R, Dell'Omo G, Nuti M, et al. Heterogeneous effect of calcium antagonists on leg edema: a comparison of amlodipine versus lercanidipine in hypertensive patients. *J Hypertens*. 2003; 21:1969-1973.
- Galappatthy P, Waniganayake YC, Sabeer MI, et al. Leg edema with (S)-amlodipine vs conventional amlodipine given in triple therapy for hypertension: a randomized double-blind controlled clinical trial. *BMC Cardiovasc Disord*. 2016; 16:168.
- Staessen JA, Bieniaszewski L, Buntinx F, et al. The trough-to-peak ratio as an instrument to evaluate antihypertensive drugs. The APTH Investigators. Ambulatory Blood Pressure and Treatment of Hypertension Trial. *Hypertension*. 1995; 26:942-949.
- Redon J. The importance of 24-hour ambulatory blood pressure monitoring in patients at risk of cardiovascular events. *High Blood Press Cardiovasc Prev*. 2013; 20:13-18.
- Parati G, Omboni S, Rizzoni D, Agabiti-Rosei E, Mancia G. The smoothness index: a new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. *J Hypertens*. 1998; 16:1685-1691.
- Palatini P, Malacco E, Di SS, et al. Trough: peak ratio and smoothness index in the evaluation of 24-h blood pressure control in hypertension: a comparative study between valsartan/hydrochlorothiazide combination and amlodipine. *Eur J Clin Pharmacol*. 2002; 57:765-770.

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