Original Research Article

A Real World Clinical Experience with S-Amlodipine in Mongolian Patients for the Management of Hypertension

Abstract:

Objective: To evaluate the efficacy and safety of S-Amlodipine in patients suffering from hypertension.

Materials and Methods: A multicenter, prospective, open-label, non-comparative, clinical study was conducted on 364 patients with hypertension in Mongolia. All these patients were treated with S- Amlodipine 2.5 mg or 5 mg orally once daily for a duration of 8 weeks.

Results: S-Amlodipine treatment resulted in a considerable drop in blood pressure from baseline. After 8 weeks of treatment, the mean systolic blood pressure had decreased by 12.06 mmHg and the mean diastolic blood pressure had decreased by 8.77 mmHg. Furthermore, both physicians and patients assessed the overall global efficacy and rated it as good. Also, during the therapy period, 6 individuals (1.7%) experienced minor or slight adverse symptoms such as cough and headache.

Conclusion: The current study confirms that treatment with S-Amlodipine was effective and well-tolerated in the management of hypertension.

Keywords: Hypertension, S-Amlodipine, Blood Pressure, Amlodipine, Mongolia, Cardiovascular Diseases.

Introduction:

Hypertension is a non-communicable disease marked by persistently high blood pressure (BP) in the systemic arteries. It is recognized as a major public health issue that raises the risk of stroke, ischemic heart disease, other vascular disorders, and kidney disease around the world. According to the World Health Organization (WHO), the number of individuals living with hypertension in the world has doubled from 650 million to 1.28 billion in the last thirty years[1]. Lowering blood pressure can reduce the number of strokes by 35%-40%, heart attacks by 20%-25%, and heart failure by around 50%[2].

Burden of Hypertension in Mongolia

As per the World Health Organization (WHO), Mongolia's average life expectancy is 68.0 years, which is much lower than that of other Asian countries such as South Korea (78.8 years) and

Japan (82.2 years). In Mongolia, hypertension is the most common cause of CVD morbidity and the third most common cause of CVD mortality[3]. As per the Mongolia Hypertension Fact Sheet by WHO (2019), 23.6% of the adult population has hypertension, while among the hypertensive patient's prevalence of uncontrolled hypertension is around 67%[4] (Figure 1 & Figure 2). According to the updated guidelines by Ministry of Health, Mongolia (2018) and American Heart Association (AHA) (2017), the threshold for hypertension is considered to be 130/80 mmHg.

Figure 1: Burden of Hypertension in Mongolia

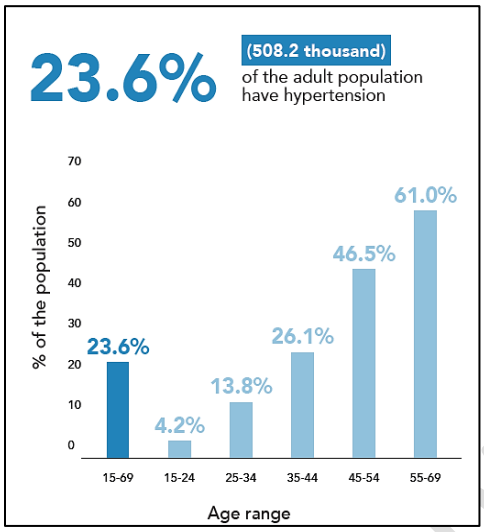
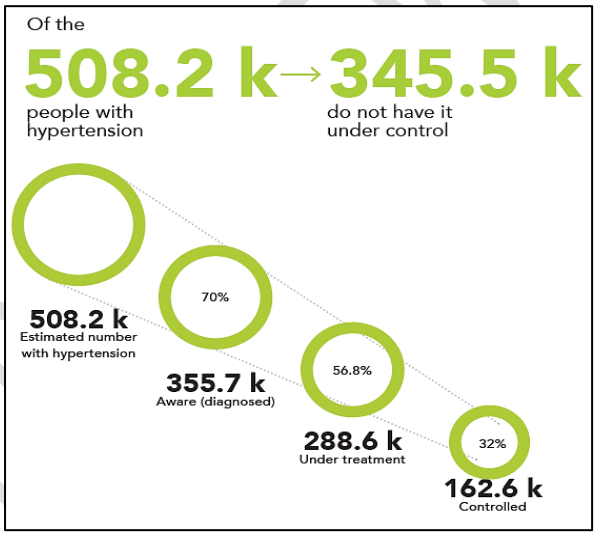


Figure 2: No. of patients with Hypertension and under treatment in Mongolia



Hypertension is a primary risk factor for stroke, and precedes hemorrhagic stroke in as many as 80% of all cases. As a result, hypertension is a critical public health issue in Mongolia, which has one of the highest rates of hemorrhagic stroke death in the world. The most significant barrier to hypertension control is a lack of hypertension awareness, especially among the young men. Also, more than half of hypertensive men under the age of 50 were unaware about the condition[5]. Several factors, such as nutritional factors, sedentary lifestyle, socioeconomic position, and environmental factors, may have influenced the prevalence of hypertension in this country[3].

New Approach in the Management of Hypertension

Various classes of antihypertensive agents such as diuretics, β-blockers (BB), α blockers, calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) are used as monotherapy or in combination for the management of hypertension[6].

Among the medications for the management of HTN, CCBs are one of the first-line agents, along with thiazide diuretics or ARBs, as recommended by Joint National Committee 8 (JNC-8)

and the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines. By lowering peripheral vascular resistance, CCBs lower arterial pressure, thereby reducing systolic and diastolic blood pressure. Furthermore, because of their effects on myocardial oxygen supply and demand, they are also effective as antianginal drugs. By dilation of the coronary arteries, all CCBs increase myocardial oxygen supply[7].

CCBs are often classified into two major categories, either non-dihydropyridines or dihydropyridines. Dihydropyridine (DHP) CCBs tend to be more potent vasodilators than non-dihydropyridine (non-DHP) agents, whereas the latter have more marked negative inotropic effects[8].

Dihydropyridine CCBs are a class of powerful, well-tolerated, and safe drugs widely used to manage elevated blood pressure (BP) as a monotherapy or as a key component of combination therapy for hypertension[6].

Amlodipine is a third-generation dihydropyridine CCB indicated to treat hypertension and angina. Apart from the high degree of selectivity for vascular smooth muscle, racemic Amlodipine also exhibits unique pharmacokinetic properties (e.g., long $t_{1/2}$). As a result, racemic Amlodipine has become one of the most commonly used antihypertensive agents[9].

S- Enantiomer of Amlodipine: Insights

Amlodipine exhibits chirality which means it has two isomers. Conventionally used Amlodipine is a racemic combination that comprises both (R) - and S-Amlodipine isomers in a 1:1 ratio, but only S-Amlodipine, as the active moiety have a therapeutic effect. According to pharmacologic studies, racemic Amlodipine reduces blood pressure by blocking the L-type calcium channel in cell membranes. This activity is seen in S-Amlodipine, but not in (R)-Amlodipine. Therefore, a formulation composed of only S-Amlodipine was developed. S-Amlodipine's usual dose is half that of racemic Amlodipine. Thus, the dose equivalency of Amlodipine and S-Amlodipine is in the ratio of 1:0.5. S-Amlodipine reduces blood pressure more effectively than R-Amlodipine[9].

From R- and S-isomers of Amlodipine, S-enantiomer has nearly 1000 times greater affinity for the receptor site. Further, S-Amlodipine has less variable pharmacokinetics, lower intrasubject variation, and a longer half-life (36–45 h). S-Amlodipine is equally efficacious at a lower doses with better tolerability and lesser incidence of peripheral edema than racemic Amlodipine[10]. Thus, the development of distinct enantiomers improves pharmacokinetics and prevents side effects like peripheral edema, which are frequent with conventional Amlodipine[9].

The purpose of this post-marketing surveillance (PMS) study was to assess the efficacy and safety of once-daily S-Amlodipine administration for the management of hypertension.

Materials and Methods:

Trial Design

A prospective, non-comparative, open-label, multicentric trial was conducted in around 6 centers in Mongolia by qualified investigators. A total of 364 patients were included who were treated with either S-Amlodipine 2.5 mg or S-Amlodipine 5 mg once daily for a duration of 8 weeks.

The treatment efficacy was assessed based on a reduction in blood pressure throughout the treatment period of 8 weeks. In addition, during the first visit, all patients' demographic information, medical history, and physical examination data were obtained. Also, at the end of the treatment, assessment of global efficacy and global tolerability was confirmed by the physicians and patients.

Patients Selection:

Inclusion Criteria: Patients with hypertension [defined as systolic blood pressure (SBP) above 140 mmHg and diastolic blood pressure (DBP) above 90 mmHg] aged 18 to 60 years old, males or non-pregnant females, were included in this study.

Exclusion Criteria: Patients with uncontrolled, high-risk hypertension (SBP ≥180mm Hg and DBP ≥110mm Hg), those who have a history of secondary hypertension and any history of suspected secondary hypertension (aortic congestion, hyperaldosteronism, renal artery stenosis, Cushing's disease, chromaffinoma, polycystic renal disease, etc.) were excluded in this study.

Treatment

All patients were given one tablet of S-Amlodipine 2.5 mg or S-Amlodipine 5 mg once a day for 8 weeks during the study period. Patients who received an initial dose of 2.5 mg of S-Amlodipine were gradually uptitrated to 5 mg of S-Amlodipine as needed.

Study Endpoints and Measures of Outcome

The efficacy of S-Amlodipine was assessed based on the rate of BP control which was determined by monitoring the SBP/ DBP mmHg on Week 8. The assessment of global efficacy and tolerability was evaluated by the physicians and patients at the end of the study. Assessment of global efficacy was rated as Very good (marked improvement), Good (moderate improvement), Satisfactory (satisfactory improvement) and Unsatisfactory (poor improvement).

Evaluation of safety was based on the occurrence of any adverse event (AE) and was graded based on the severity and onset of adverse effects.

Statistics

Statistical analysis was performed on the basis of pooled data and the results were analyzed using parametric and non-parametric tests, with a significant *p*-value of < .05.

Results

A total of 364 hypertensive patients across 6 sites were evaluated in this study. The overall patient demographic profile is presented in Table 1.

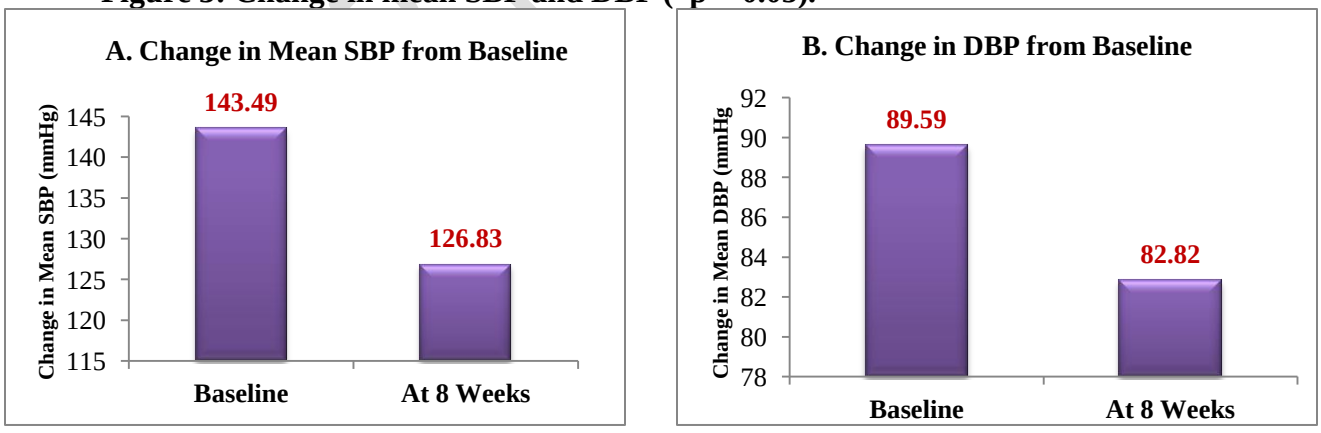
Table 1: Summary of Patient Demographic Profile

Variable	S-Amlodipine (N = 364)
Gender, n (%)	
Female	242 (66.48)
Male	122 (33.52)
Age Years/ Overall	
Mean (Standard Deviation)	55.43 (12.65)
Minimum – Maximum	24 - 78
Weight Kg/ Overall	
Mean (Standard Deviation)	72.47 (12.07)
Minimum – Maximum	43 - 110

Effect on Blood Pressure

Mean SBP at baseline was 143.49 mmHg and mean DBP at baseline was 89.59 mmHg. A substantial difference in BP was observed after the study treatment. After 8 weeks of treatment the mean change in SBP and DBP were 126.83 mmHg and 82.82 mmHg respectively from baseline, p = .05 (Figure 3). The change in mean SBP and DBP was found to be statistically significant.

Figure 3: Change in mean SBP and DBP (*p < 0.05).



Dosage Change during the Treatment Period

During the treatment, approximately 19 (5%) of patients on S- Amlodipine 2.5 mg required dose escalation from 2.5 mg to 5 mg.

Global Assessment of Efficacy of Treatment

As per physician's evaluation, 34.54% and 40.11% of cases showed very good and good improvement (Figure 4a) after 8 weeks of treatment. According to patient's evaluation, 31% of the patients had very good and 49% had good improvement (Figure 4b)

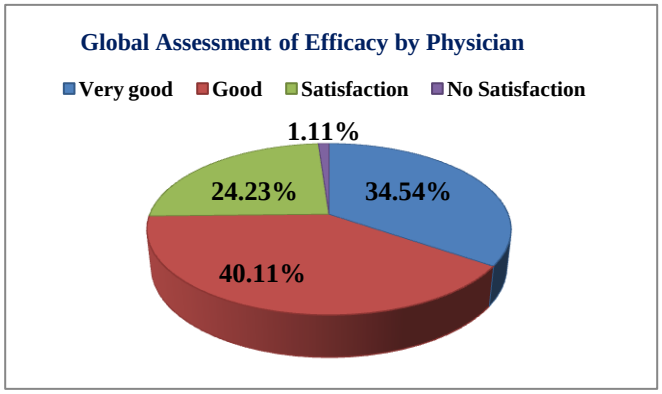


Figure 4a: Global Assessment of Efficacy by Physician

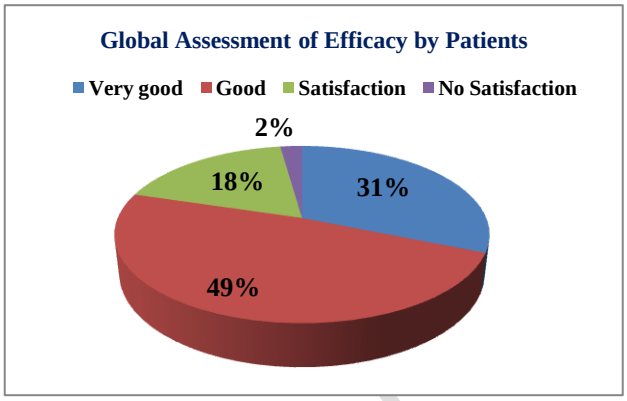


Figure 4b: Global Assessment of Efficacy by Patients

Safety Assessment

This study reveals that 1.7% of the total cases had adverse events. The reported adverse effects include cough and headache with mild intensity. In addition, according to the study, there were no incidences of pedal edema among these patients.

Discussion

Hypertension is widely recognized as the leading cause of death and disease worldwide. The global burden of hypertension has been increased over time, owing primarily to lifestyle changes and aging. Inadequate BP control is strongly, independently, and linearly associated with the risk of CVD, CKD, and all-cause mortality[11].

High BP has several negative consequences. Increase in a 20/10 mmHg elevation from 120/80 mmHg are linked to a 35% increased risk of ischemic stroke, 29% increased risk of myocardial infarction and the risk of end-stage renal disease increases by 2.6-fold. Thus, Guidelines suggest aggressive hypertension management based on the findings of the SPRINT (Systolic Blood Pressure Intervention Trial)[12].

The ultimate goal of antihypertensive therapy is cardiovascular risk reduction. As decreasing blood pressure alone reduces the risk of myocardial infarction by 20% to 25%, it is apparent that better protection is required. An optimal strategy to minimize the risk of hypertension may include lifestyle modification, promotion of adherence to therapy, and early and aggressive target levels achievement by appropriate drug choice[2].

Conventionally used Amlodipine is a racemic combination of R- and S-Amlodipine isomers. Pharmacologic studies show that racemic Amlodipine decreases BP by blocking the L-type calcium channel in cell membranes. In fact, S-Amlodipine has this activity but (R)-Amlodipine does not. In addition, S-enantiomer has nearly 1000 times greater affinity for the receptor site when compared to conventional Amlodipine[9].

The vasoactive enantiomer of Amlodipine, S-Amlodipine in clinical trials, has been shown to be effective in the treatment of hypertension. Also, the pharmacokinetics, pharmacodynamics, and

safety profiles of S-Amlodipine versus racemic Amlodipine were comparable in many studies. It is also reported that S-Amlodipine 2.5 mg and S-Amlodipine 5 mg are bioequivalent in terms of absorption and elimination and that they are similar in controlling BP and in tolerability. Similar outcomes have been obtained in the studies comparing S-Amlodipine 5 mg and racemic Amlodipine 10 mg. Therefore, in the treatment of hypertension, a single dose of S-Amlodipine 2.5 mg is indicated as the initial dose, and depending on the patient's response, the dose can be titrated to a maximum of 5 mg/day[13]. Also, S-Amlodipine was effective in 24-hour ambulatory BP reduction, including day-time and night-time BP reduction[9].

Pathak. L et al. conducted a randomized trial in 200 hypertensive patients for six weeks and revealed that the difference in the average reduction in systolic and diastolic blood pressures in the two treatment groups, in the sitting, supine and standing positions was not found to be statistically significant. Thus, it was concluded that S-Amlodipine 2.5 mg is equivalent in its efficacy and tolerability when compared to Amlodipine 5 mg in the treatment of mild to moderate hypertension[14].

The present study, which was conducted to evaluate the efficacy and safety of S-Amlodipine at a daily dose of 2.5 mg/5 mg on blood pressure control in adult hypertensive patients, found that both mean SBP and DBP levels significantly decreased at the end of 8 weeks.

Based on the findings of this study, it was determined that S-Amlodipine is an effective therapeutic option in hypertensive patients at doses of 2.5 mg/5 mg.

The majority of physicians and patients rated the global treatment efficacy with S-Amlodipine as good, confirming the utility of S-Amlodipine's in hypertension management. The mean SBP reduced by 12.06 mmHg, and the mean DBP reduced by 8.77 mmHg by the end of 8 weeks.

The threshold for hypertension is considered 130/80 mmHg, which is in tune with hypertension guidelines published by the American Heart Association (AHA) in 2017 and guidelines by the Ministry of Health, Mongolia (2018).

The current study results from Mongolian hypertensive patients were in tune with a study by *Sen. S. et al.* to assess the efficacy and safety of S-Amlodipine 2.5 mg and 5 mg once daily for 8 weeks in patients with hypertension who were either treatment-naive or had previously received antihypertensive monotherapy. The study found that S-Amlodipine 2.5 mg/d resulted in a significant reduction in BP, and significant reductions in both office and ambulatory BPs were achieved with dose titration (5 mg/day). Furthermore, both office and ambulatory BP levels attained with S-Amlodipine 2.5 mg/5 mg in the antihypertensive monotherapy group were typically non-inferior to both office and ambulatory BP levels achieved with the medications that the patients received before participating in the trial. There was also a favorable safety profile, with no serious adverse events reported[13].

Another study by *Chen et al.,* conducted an 8-week randomized trial on patients with mild or moderate hypertension to investigate the efficacy and tolerability of initial low (2.5 mg/day) vs. high (5 mg/day) doses of S-Amlodipine (equivalent to 5 and 10 mg of racemic amlodipine, respectively), found that the 24-hour ambulatory SBP/DBP value decreased significantly from baseline at the eighth week. Furthermore, the initial low dose of S-Amlodipine improved 24-hour ambulatory blood pressure control with tolerance comparable to an initial high dose in hypertension[15].

Also, S-Amlodipine is internationally approved and available in fixed dose combinations with other commonly used antihypertensive drugs such as ARBs like Telmisartan, Diuretics like Hydrochlorothiazide, and Beta-blockers such Atenolol for the management of hypertension. *Galappatthy P et al*. investigated the incidence of leg edema as a primary outcome and antihypertensive efficacy of S-Amlodipine compared to conventional Amlodipine in hypertensive patients not controlled on prior BB and ACEI/ARB therapy. The study revealed that adding S-Amlodipine at half the dose of conventional Amlodipine significantly reduced incidence of peripheral edema and provided equal antihypertensive efficacy compared to Amlodipine at usual doses[16].

The development of separate enantiomers improves pharmacokinetics (PK) and avoids undesirable AEs. The most common reason for poor adherence with Amlodipine is the occurrence of peripheral edema. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) reported peripheral edema in 23% of Amlodipine-treated individuals. This implies that approximately one in every four individuals treated with Amlodipine may develop peripheral edema[10].

In order to assess the benefits of reducing pedal edema, the SESA trial discovered that edema resolved in 98.72% of patients after switching from racemic Amlodipine to S-Amlodipine. Another study, SESA-II, in 2230 HTN patients found that 41.90% had pedal edema on racemic Amlodipine before switching to S-Amlodipine, with 93.07 % reduction with a 1.92% total incidence of pedal edema with S-Amlodipine. Therefore, the use of chirally pure S-Amlodipine would be favorable due to the lesser risk of edema, leading to better adherence to therapy and hence better blood pressure control[10].

In the current PMS study, treatment with S-Amlodipine was well tolerated, with no significant adverse effects being experienced by the patients. Although cough and headache were the most rare reported adverse effects, the severity of these adverse effects was graded as minor during therapy. Also, no patients reported pedal edema during the study period.

Conclusion:

This study reveals the significant and clinically relevant effect of S- Amlodipine on blood pressure reduction with lower adverse effects. Thus, it may be considered among the first-line antihypertensive agents in Mongolian patients for the management of hypertension.

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