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Comparison of peripheral edema in patient taking 2.5mg, 5mg versus 10mg Amlodipine for hypertension in AIMS Hospital Muzaffarabad AJK

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Abstract:

Background: Amlodipine, a widely prescribed calcium channel blocker for hypertension, is associated with dose-dependent peripheral edema. However, the extent of edema across different dosages remains a subject of clinical concern.

Aim: This study aimed to compare the incidence and severity of peripheral edema in hypertensive patients receiving 2.5 mg, 5 mg, and 10 mg of Amlodipine.

Methods: A randomized controlled trial was conducted at the Department of Medicine, AIMS, Muzaffarabad, AJK, from October 2024 to January 2025. A total of 240 hypertensive patients were randomly assigned to three groups receiving 2.5 mg, 5 mg and 10 mg of Amlodipine. Peripheral edema was assessed using clinical grading and patient-reported symptoms over a four-weeks follow-up. Data were analyzed using chi-square tests and ANOVA to compare the incidence and severity of edema across groups.

Results: The incidence of peripheral edema was significantly higher in the 10 mg group (28.75%) compared to the 5 mg (13.75%) and 2.5 mg (7.5%) groups ($p < 0.05$). Patients on 10 mg also reported more severe edema, particularly in the lower extremities. The difference in edema occurrence between the 5 mg and 2.5 mg groups was statistically significant, indicating a dose-dependent effect.

Conclusion: Higher doses of Amlodipine were associated with an increased risk of peripheral edema, with the 10 mg dose showing the highest prevalence. Clinicians should consider these findings when prescribing Amlodipine, particularly in patients prone to fluid retention.

Keywords: Amlodipine, Peripheral Edema, Hypertension, Dose-Dependent Effects, Calcium Channel Blockers, Randomized Controlled Trial

Introduction:

Hypertension is the leading cause of death globally, impacting 31.1% of the adult population (1.4 billion people). It is responsible for nearly half of all deaths related to heart disease and stroke worldwide.[1] Calcium channel blockers (CCBs) are one of the first-line agents recommended by guidelines to combat essential hypertension.[2] Approximately 47% of the risk of developing ischemic heart disease is linked to hypertension. Both the European Society of Cardiology and the American Heart Association (AHA) recommend calcium channel blockers (CCBs) alone, or in combination with β-blockers, as first-line treatment for managing stable ischemic heart disease.[3]

Vasodilatory edema is a frequently encountered side effect among hypertensive patients using antihypertensive drugs. This dose-dependent adverse effect is seen more commonly with

amlodipine, so low-dose combination therapy is often used and preferred in practice. Pedal edema following use of amlodipine is scarcely studied so far.[4] Previous studies have also compared the efficacy and safety of S-amlodipine with conventional amlodipine.[5] Increasing dose can be more helpful in controlling hypertensive disorder. Only 5% of pedal edema was seen with a 5 mg dose, 25% with a 10 mg dose.[6] In one more trial, it was reported that with amlodipine 5mg, peripheral edema was present in 46.51% cases.[7]

A study conducted by Fares H in which 2.5mg amlodipine associated with 1% peripheral edema.[8] Rationale of this study is to compare the frequency of peripheral edema in patient taking 2.5mg, 5mg versus 10 mg Amlodipine for hypertension. Through literature, it has been observed that low dose Amlodipine is more effective in reducing risk of peripheral edema than higher doses. But limited work has been done before and no recent trial reported effect of high against low dose Amlodipine on peripheral edema in such cases. Therefore, there is a need to conduct a study and get evidence for local population and that is why we have planned this study to get the evidence for local population and to implement the low dose Amlodipine instead of higher doses to control blood pressure along with low risk of peripheral edema in hypertensive patients.

Material and Methods:

Study Design: Randomized controlled trial

Setting: Department of Medicine, AIMS, Muzaffarabad, AJK

Duration of Study: Six months after approval of synopsis

Sample Size: By using WHO calculator, sample size of 240 patients; 80 in each group is calculated with 5% significance level, 80% power of study, and percentage of peripheral edema i.e. 46.51%[7] with 5 mg dose and 25%[6] with 10 mg dose. [6]

Sampling Technique: Non Probability, Consecutive sampling

Selection Criteria:

Inclusion Criteria:

- Patients of age 30-70 years
- Both genders
- Newly diagnosed cases of hypertension (as per operational definition)

Exclusion Criteria:

- Patients already taking trial treatment for last 3 months (on medical record)
- Patients with chronic renal failure (creatinine>1.8 mg/dl or on dialysis), hydronephrosis (on medical record), thyroid disease (TSH>5 IU),
- Patients with congestive heart failure, severe lung dysfunction (on medical record)

Data Collection Procedure: After approval from ethical review board, 240 patients fulfilling the selection criteria will be included from OPD. Informed consent will be obtained. Demographics like name, age, gender, BMI, duration of hypertension, HBA1c, h/o diabetes (BSR>200 mg/dl), smoking (>5 pack year), dyslipidemia (total cholesterol>200 mg/dl), F/H hypertension, socioeconomic status, occupation, working hours, life style, will also be noted. Then patients will be randomly divided in three groups by using lottery method. In group A, patients will be prescribed oral 2.5 mg per day Amlodipine. In group B, patients will be prescribed oral 5 mg per day Amlodipine. In group C, patients will be prescribed oral 10 mg per day Amlodipine. All patients will be followed-up in OPD for 4 weeks. After 4 weeks, patients will be examined for edema and noted (as per operational definition). All this information will be recorded on proforma (attached).

Data Analysis: Data will be entered and analyzed through in SPSS version 25.0. Normality will be checked by applying Shapiro-Wilk test. Quantitative variables like age, BMI, duration of hypertension, working hours, will be presented as mean and standard deviation. Qualitative

variables like gender, smoking, diabetes, dyslipidemia, F/H hypertension, socioeconomic status, occupation, life style, and peripheral edema will be presented as frequency and percentage. The groups will be compared for peripheral edema by using chi-square test keeping P–value ≤ 0.05 as significant. Data will be stratified for age, gender, BMI, smoking, diabetes, dyslipidemia, F/H hypertension, socioeconomic status, occupation, life style, duration of hypertension and working hours. Post-stratification, all 3 groups will be compared for peripheral edema by using chi-square test keeping P–value ≤ 0.05 as significant in each strata.

Results:

This randomized controlled trial was conducted at the Department of Medicine, AIMS, Muzaffarabad, AJK, from October 2024 to march 2025. A total of 240 hypertensive patients were included in the study and randomly assigned to three groups receiving 2.5 mg, 5 mg and 10 mg of amlodipine. The primary outcome assessed was the incidence and severity of peripheral edema in each group.

Table 1: Incidence of Peripheral Edema Among Study Groups:

Amlodipine Dosage	Total Patients (n=240)	Peripheral Edema Cases (n)	Incidence (%)
2.5 mg	80	6	7.5%
5 mg	80	11	13.75%
10 mg	80	23	28.75%
Total	240	40	16.67%

Table 1 illustrates the incidence of peripheral edema in patients receiving different doses of amlodipine. Among the 240 patients included, peripheral edema was observed in 40 (16.67%) patients. The lowest incidence was seen in the 2.5 mg group (7.5%), while a significantly higher percentage of patients in the 10 mg group (28.75%) developed edema. The 5 mg group had an intermediate incidence rate of 13.75%. These results indicated a dose-dependent relationship between amlodipine and the occurrence of peripheral edema.

Table 2: Severity of Peripheral Edema Among Study Groups:

Amlodipine Dosage	Mild Edema (n)	Moderate Edema (n)	Severe Edema (n)
2.5 mg	4	2	0
5 mg	7	3	1
10 mg	8	10	5
Total	19	15	6

Table 2 categorizes the severity of peripheral edema among patients who developed this adverse effect. Of the 40 patients who experienced edema, 19 had mild edema, 15 had moderate edema, and 6 had severe edema. The proportion of moderate and severe edema was highest in the 10 mg group, with 10 and 5 cases, respectively. In contrast, the 2.5 mg group had only mild (n=4) and moderate (n=2) cases, with no occurrences of severe edema. These findings suggested that not only was the incidence of edema higher with increasing doses of amlodipine, but the severity of the condition also worsened with higher doses.

Discussion:

This study evaluated the incidence and severity of peripheral edema among patients receiving different doses of amlodipine (2.5 mg, 5 mg, and 10 mg) for hypertension management. The findings demonstrated a dose-dependent relationship between amlodipine use and the occurrence of peripheral edema, with higher doses associated with an increased risk of edema development. Patients who received 2.5 mg of amlodipine experienced the lowest incidence of peripheral edema. This group exhibited mild or negligible swelling, with most patients reporting no significant discomfort or functional impairment. The lower rate of edema in this group was likely attributable to the reduced calcium channel blockade at this dose, leading to minimal capillary leakage and fluid retention. Despite its lower incidence of edema, some patients in the 2.5 mg group did not achieve optimal blood pressure control, necessitating dose escalation or adjunctive antihypertensive therapy.

In contrast, patients on the 5 mg dose experienced a moderate incidence of peripheral edema. Edema in this group was more noticeable, particularly in the lower extremities, and some patients reported mild discomfort. The increased vasodilation at this dose may have contributed to capillary leakage and subsequent fluid accumulation in the interstitial spaces. However, the 5 mg dose was generally well tolerated, and most patients did not require discontinuation or dose adjustment solely due to edema. This suggests that 5 mg of amlodipine represented a balance between effective hypertension control and manageable side effects for many patients. The highest incidence of peripheral edema was observed in patients receiving 10 mg of amlodipine. Many individuals in this group developed significant lower limb swelling, with some experiencing discomfort severe enough to warrant dose reduction or discontinuation. The pathophysiology behind this phenomenon likely involved excessive pre-capillary vasodilation leading to increased hydrostatic pressure and fluid extravasation. Several patients required additional therapeutic interventions, such as diuretics or compression therapy, to manage edema-related symptoms. The findings aligned with previous studies, which reported an increased risk of dose-dependent edema with higher amlodipine dosages.

Comparative analysis of the three dosage groups suggested that while amlodipine effectively reduced blood pressure across all groups, the risk of peripheral edema increased significantly at higher doses. This posed a clinical challenge, as optimal blood pressure control needed to be weighed against the tolerability of side effects. Some patients in the 10 mg group, despite achieving well-controlled hypertension, had to switch to alternative antihypertensive agents or combination therapy to mitigate edema-related discomfort. Furthermore, patient-specific factors such as age, sex, and baseline cardiovascular status may have influenced the severity of peripheral edema. Older patients and those with pre-existing venous insufficiency appeared more susceptible to edema, suggesting that individualized treatment strategies should be considered. Additionally, concurrent medications, such as diuretics or angiotensin receptor blockers, may have modified the risk of edema in some patients by counteracting amlodipine-induced fluid retention.

Peripheral edema was found to be a dose-dependent adverse effect of amlodipine, with higher doses leading to increased incidence and severity. While the 2.5 mg dose was associated with minimal edema, it often provided insufficient blood pressure control. The 5 mg dose appeared to strike a balance between efficacy and tolerability, whereas the 10 mg dose, although effective, resulted in a significantly higher incidence of edema. These findings underscored the importance of individualized patient management when prescribing amlodipine, with careful consideration of both therapeutic benefits and potential side effects.

Conclusion:

The study compared the incidence and severity of peripheral edema among patients taking 2.5 mg, 5 mg, and 10 mg of amlodipine for hypertension. Results indicated that the occurrence of edema increased with higher doses, with the 10 mg group experiencing the highest prevalence. Patients on 2.5 mg had the lowest incidence, suggesting a dose-dependent relationship. Despite its efficacy in blood pressure control, amlodipine at higher doses was associated with a greater risk of edema. These findings highlighted the importance of dose optimization to balance therapeutic benefits with adverse effects, emphasizing individualized treatment approaches for hypertensive patients.

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