

**Original Article**

**A PROSPECTIVE CLINICAL TRIAL OF AMLODIPINE IN COMPARISON TO PERINDOPRIL**

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**ABSTRACT**

**Objective:** The objective of this research was to perform a prospective clinical trial to compare antihypertensive effects of amlodipine and perindopril in hypertensive patients.

**Methods:** In our study, we compared antihypertensive effects of well tolerated and commonly used antihypertensive drugs, amlodipine and perindopril. There were 81 hypertensive patients of both sexes over 40 y of age without other diseases included in this prospective clinical trial. Forty (40) patients were treated with amlodipine (5 mg/day) and forty-one (41) patients were treated with perindopril (4 mg/day). After one month of taking both drugs, blood pressure was measured in the supine position with a standard mercury sphygmomanometer in the morning.

**Results:** Amlodipine and perindopril groups were having almost similar characteristics at the beginning of the study. There was significantly decrease insystolic blood pressure (sBP) throughout the study period in the amlodipine group ( $p \leq 0.05$ ) but not in the perindopril group. The efficacy of amlodipine over perindopril on systolic blood pressure and diastolic blood pressure (dBP) was significant ( $p \leq 0.001$  for sBP and  $p \leq 0.05$  for dBP).

**Conclusion:** It may be concluded that the antihypertensive efficacy of amlodipine was superior when compared to perindopril.

**Keywords:** Amlodipine, Perindopril, Comparative efficacy, Hypertension

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**INTRODUCTION**

Clinically, hypertension is defined as that level of blood pressure (BP) at which the institution of therapy reduces blood pressure related morbidity and mortality [1]. According to British Hypertension Society (BHS) blood pressure is categorized by BP <120/80 mmHg is optimal, <130/85 mmHg is normal, 130-139/85-89 mmHg is high normal, grade-1 hypertension (mild) is 140-159/90-99 mmHg, grade-2 (moderate) is 160-179/100-109 mmHg, grade-3 (severe) is systolic  $\geq 180$  and diastolic >110 mmHg [2]. Antihypertensive drugs are being used tremendously since long time ago. In Bangladesh, the prevalence of hypertension was 14.4% with systolic blood pressure (sBP)  $\geq 140$  mmHg and 9.1% with diastolic blood pressure (dBP)  $\geq 90$  mmHg. Studies from India and Bangladesh have shown an upward trend in the prevalence of hypertension [3]. For developing countries it is one of the most vital problems and if left untreated leading serious and life threatening conditions [4] of the body like heart disease, stroke, end-stage renal failure, and peripheral vascular disease. Antihypertensive treatment can decrease the rate of cardiovascular morbidity and mortality [5] also alleviates the progression of chronic kidney disease [6].

In United States, 77% of adults with hypertension used at least one antihypertensive medication in large scale of survey [7]. During last 20 y; several major therapeutic advances have markedly improved the prognosis of patients with coronary artery disease (CAD) [3]. There are 5 classes of drugs used for the treatment of hypertension and prevention of cardiovascular morbidity [5]. Among these drugs, two of them; angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCB) were used in this study to demonstrate their beneficial effects in hypertensive patients [8]. Antihypertensive drugs amlodipine and perindopril are widely used due to the low incidence of adverse drug reaction and they are well tolerated. ACE inhibitors decrease the production of angiotensin II, increase bradykinin levels and reduce sympathetic nervous system activity [1]. Blockage of bradykinin breakdown and enhancement of prostaglandin release may probably participate in the antihypertensive activity of ACE-inhibitors [9]. Perindopril is long acting

member of ACE inhibitors. This is a prodrug and is converted to the active agent by hydrolysis, primarily in the liver [1].

Calcium channel blockers block voltage-gated calcium channels in the heart and vasculature [10]. They reduce vascular resistance, which reduces intracellular calcium and blunts vasoconstriction [1] due to long lasting relaxation of smooth muscle and a reduction in contractility throughout the heart. On heart, it also decreases SA node rate and AV nodal conduction velocity [11]. Only about one third of all hypertensive patients receiving therapy, however, have reached their goal blood pressure (<120/80 mmHg). By controlling BP can reduce the risk of developing myocardial infarction, heart failure, stroke and renal disease in hypertensive patients [12].

**MATERIALS AND METHODS**

A double-blinded, randomized, parallel-group study was conducted in the Department of Pharmacology, Sylhet MAG Osmani Medical College, Bangladesh for 30 d. Eighty-one (81) diagnosed hypertensive patients of both sexes of aged between 40 to 80 y were taken from the Department of Medicine of Sylhet MAG Osmani Medical College Hospital, Bangladesh.

Permission of research was taken from ethical committee of Sylhet Osmani Medical College. Written informed consent was obtained from each patient before starting the trial. Among 81 patients 52 were male (64.2%) and 29 were female (35.8%). The patients were randomly allocated to treatment with either amlodipine 5 mg once a day (n=40) or perindopril 4 mg once a day (n=41), for 30 d. Hypertensive patients with other co-morbidities like diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and renal failure (RF) were excluded from the study. Then, data were collected by using a pre-diagnosed questionnaire. Blood pressure was measured with a standard mercury sphygmomanometer in the supine position in the morning and safety assessments were made throughout the study period.

**Statistical analysis**

All the data were presented as mean  $\pm$  standard deviation (SD) at 95% confidence interval (CI<sub>0.95</sub>). Statistical analysis was done by applying unpaired t-test using Graph pad prism software version 5.0.

## RESULTS

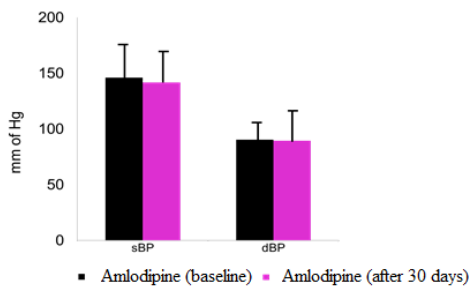
Baseline characteristics were almost similar in both study drug groups shown in table 1. In amlodipine study group, total subjects were 40 (male and female ratio was 22/18) whereas, in perindopril study group total subjects were 41 (male/female ratio was 30/11). At the beginning of the study lying sBP in both amlodipine and perindopril groups were  $146.13 \pm 12.88$  mmHg and  $149.27 \pm 12.97$  mmHg respectively and lying dBP were  $90.50 \pm 6.28$  mmHg and  $89.76 \pm 5.36$  mmHg respectively. The sBP and dBP changes within same study

groups are depicted in (fig. 1). There was significant decrease of sBP in amlodipine treated group after 30 d, but no significant reduction of dBP. The sBP and dBP in perindopril treated group were not reduced and tentative to increase (fig. 2). The comparative antihypertensive efficacy of amlodipine and perindopril (fig. 3). There were significant differences of both sBP (amlodipine  $141.58 \pm 12.52$  mmHg, perindopril  $152.93 \pm 16.92$  mmHg) ( $p \leq 0.001$ ) and dBP (amlodipine  $89.38 \pm 7.44$  mmHg, perindopril  $92.76 \pm 7.96$  mmHg) ( $p \leq 0.05$ ) after 30 d. There was obviously seen that amlodipine decreased BP more effectively ( $p \leq 0.001$ ) than dBP.

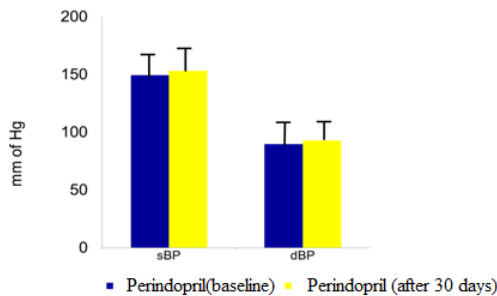
**Table 1: Demographic characteristics of the two studied groups**

Study parameters	Amlodipine mean $\pm$ SD <sup>a</sup>	Perindopril mean $\pm$ SD <sup>a</sup>
Age (Years)	54.10 $\pm$ 9.49	55.56 $\pm$ 10.09
Weight (Kg)	64.03 $\pm$ 6.39	68.32 $\pm$ 4.77
Lying systolic BP (mm Hg)	146.13 $\pm$ 12.88	149.27 $\pm$ 12.97
Lying Diastolic BP (mm Hg)	90.50 $\pm$ 6.28	89.76 $\pm$ 5.36

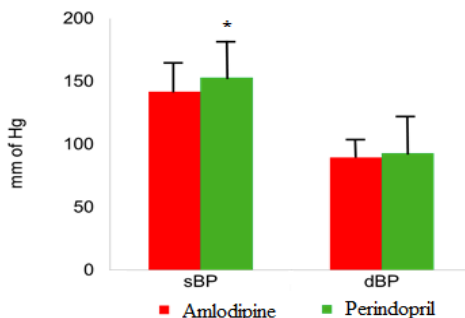
The number of subjects selected for study n= 81 (amlodipine N=40, perindopril N=41). a= mean $\pm$ Standard deviation (SD)



**Fig. 1: Comparison of systolic blood pressure (sBP) and diastolic blood pressure (dBP) changes in mean $\pm$ standard deviation in amlodipine studied group (N=40) at baseline and after 30 d of treatment**



**Fig. 2: Comparison of systolic blood pressure (sBP) and diastolic blood pressure (dBP) changes in mean $\pm$ standard deviation in perindopril studied group (N=41) at baseline and after 30 d of treatment**



**Fig. 3: Comparison of systolic blood pressure (sBP) and diastolic blood pressure (dBP) changes in mean $\pm$ standard deviation between amlodipine and perindopril studied group (n=81) after 30 d of treatment**

## DISCUSSION

Hypertension is an important worldwide public health challenge [13] which is associated with an increased risk of cardiovascular mortality, stroke and renal disease. So, controlling of blood pressure is essential for the prevention of high BP related morbidity on a long-term basis [14-16]. Although lifestyle modification can improve for managing hypertension, antihypertensive drug therapy is still needed for most hypertensive patients to control BP within normal limit [7]. There are many drugs for initial treatment of essential hypertension. Considering side effects, drug interactions and comorbid conditions, drugs like thiazide diuretics, ACE inhibitors, Angiotensin Receptor Blockers (ARBs), CCBs and  $\beta$ -blockers are used as first line drugs for the treatment of hypertension. Trials compared thiazide diuretics, ACE inhibitors, ARBs and CCBs did not show consistent differences in outcome, efficacy, side effects or quality of life.  $\beta$ -blockers which are previously used as a first line therapy, have a weaker evidence base. Combination drug therapy has more advantageous than single drug therapy because of lesser side effects. In a study, it was evidenced that perindopril protected cardiovascular (CV) events of hypertensive patients in combination with other antihypertensive drugs. When perindopril was combined with either amlodipine or indapamide, maximal reduction of BP resulted in decreased CV deleterious effects [16]. CCB and ACE inhibitors might be the suitable combination in treating hypertension when ACE inhibitors monotherapy is not sufficient to control BP [17]. Though, initially single drug with lower initial doses are better tolerated, cost effective and have better compliance.

In our study, two commonly used drugs were compared on 81 hypertensive patients. Amlodipine was given to 40 patients, 5 mg/day and perindopril to 41 patients, 4 mg/day. Amlodipine reduced both sBP and dBP from baseline. Amlodipine in compare with perindopril significantly reduced sBP ( $p \leq 0.001$ ) after one month but both drugs were well tolerated. Most frequent adverse effect of amlodipine was leg oedema (10.2%) and perindopril was coughing (12.5%). The result was comparable with some similar studies [18-19]. Zannad, Bernaud and Fay (1999) assessed the efficacy of amlodipine and perindopril [18] by Trough: Peak ratio from 24h ambulatory BP recordings, before and after active treatment period (60 d). Both treatment groups produced comparable reduction in clinical sBP and dBP between '0' and '60' days. Both sBP and dBP were lowered in amlodipine treated patients than perindopril 48 h after last dose. Most frequent adverse effect was leg oedema in amlodipine (19.1%) and coughing in perindopril (14.3%). After omitting one dose, a condition imitating noncompliance, BP was more effectively controlled by amlodipine than perindopril.

Eguchi *et al.*, (2004) compared Valsartan (an ARB) and amlodipine (CCB). In that study both drugs significantly reduced sBP and dBP ( $p < 0.002$ ) [19]. Antihypertensive effect of amlodipine was superior

to valsartan. Morning sBP was significantly reduced by amlodipine from 156 to 142 mmHg ( $p < 0.001$ ) but not by valsartan. Both agent reduced lowest night sBP to a similar extent (amlodipine 121 to 112 mmHg,  $p < 0.001$ ; valsartan 123 to 114 mmHg,  $p < 0.002$ ). Reduction of morning sBP surge (morning sBP minus lowest night sBP) was significantly greater in patients treated with amlodipine compared those treated with valsartan (-6.1 mmHg vs +4.5 mmHg,  $p < 0.02$ ). Amlodipine monotherapy was more effective than valsartan monotherapy in controlling 24 h ambulatory BP and morning BP in hypertensive patients.

### CONCLUSION

In conclusion, our study showed that amlodipine has better efficacy than perindopril as initial monotherapy. It was suggested that amlodipine is the drug of choice in controlling BP in mild to moderate hypertension when compared with perindopril. Further studies are required comparing other antihypertensive drugs and with increased sample size to identify the risks and benefits of amlodipine to prove its efficacy compared to other antihypertensive drugs as monotherapy in mild to moderate hypertension.

### Study limitation

In our study the number of patients was limited (81) and the study duration was only one month.

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### CONTRIBUTION OF AUTHORS

I declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dr. Suprava Das and Dr. Myat Thu Thu Win and Dr. Sherly Deborah G collected and analysed the data, Dr. Lubna Shirin and Dr. Mohammad Shahjahan Kabir designed the study and Dr. Sridevi Chigurupati helped in writing the manuscript and statistical calculations.

### CONFLICTS OF INTERESTS

Declared none

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