COMPARATIVE STUDY ON ANTI-HYPERTENSIVE EFFECTS OF AMLODIPINE AND ENALAPRIL IN PRIMARY HYPERTENSION

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Summary

A prospective, randomized study was conducted at two Nepalese hospitals to compare the mean reduction in Blood Pressure (BP), Pulse Rate (PR) and Adverse Drug Reactions (ADRs) caused by amlodipine and enalapril. Thirty-six patients each in amlodipine and enalapril group were followed at 0, 1, and 4 weeks. Median age of the patients was 46.5 years and only 40% had schooling. Overall, 50% were either current or past smokers, 5.56% diabetic and 26.39% had family history of hypertension. Systolic/diastolic BP reduction in enalapril group was significant after 1 week (P = 0.000, 0.000) and insignificant after 4 weeks (P= 0.131, 0.271). In amlodipine group systolic/diastolic BP reduction was significant after 1 week (P = 0.000, 0.000) and after 4 weeks (P = 0.000, 0.008). BP reduction with enalapril was statistically insignificant (P = 0.618, 0.289). Enalapril decreased PR significantly (P = 0.004) after 1 weeks and insignificantly after 4 weeks (P = 0.803). Amlodipine decreased PR insignificantly after 1 and 4 weeks (P = 0.071, 0.556). PR reduction was more in enalapril group and was significant (P = 0.041, 0.025). Dry cough, nausea and dizziness were major ADRs with enalapril; whereas, peripheral edema, nausea and shortness of breath with amlodipine. More number of ADRs was experienced with amlodipine and 2 patients needed a change in drug therapy due to ankle edema. Both drugs were equally effective in terms of BP reduction and enalapril was better tolerated.

Keywords: Amlodipine, Comparative study, Efficacy, Enalapril, Hypertension, Safety.

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Introduction

Hypertension is one of the most common diseases affecting humans worldwide. It is the most common disease-specific reason for which patients visit a physician. It is currently among the leading cause of morbidity and mortality throughout the world. About half of the world's cardiovascular burden is predicted to occur in Asia Pacific region [1]. Globally, approximately two-thirds of stroke and one-half of ischemic heart disease were attributable to non-optimal blood pressure [2]. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and 7.1 million deaths were estimated to be due to hypertension [3]. Prevalence of hypertension varied around the world, with the lowest prevalence in rural India (3.4% in men, 6.8% in female) and the highest prevalence in Poland (68.9% in men and 72.5% in female) [4]. The prevalence of hypertension according to new criteria (>140/90 mmHg) varies between 15-35% in urban adult populations of Asia [5]. The prevalence of hypertension in Nepal at present is 19.7% [6].

Apart from lifestyle modification, several pharmacological agents are available to treat the hypertension [7, 8, 9] that include angiotensin converting enzyme (ACE) inhibitors, beta blockers (BBs), calcium channel blockers (CCBs), diuretics, alpha blockers, angiotensin II receptor blockers, central alpha-2 agonists, adrenergic inhibitors, and vasodilators. A study identified that in Nepal the most frequently prescribed ACE inhibitors and calcium channel blockers are enalapril and amlodipine respectively [10]. However, studies comparing the efficacy and safety of these drugs are scarce and those available are conducted in the western population. The data are lacking in south Asian population. So, the present study was conducted with the following objectives.

1. To compare the mean reduction in BP and pulse rate by amlodipine and enalapril in hypertensive patients.

2. To compare the adverse drug reaction (ADR) associated with amlodipine and enalapril in the study population

Methodology

Study materials: The following materials were used in the study.
1. Patient profile form: This was developed manually by the researchers. The duly filled form contains patient's information, past medical and medication history, patient complaints and diagnosis. It also contains the monitoring parameters like BP, pulse rate and some common adverse effects.
2. Blood Pressure apparatus: Mercury Sphygmomanometer was used to measure BP of the study population.

Study site: The study was conducted at the following sites:
1. Kathmandu University Teaching Hospital (KUTH) Dhulikhel: KUTH is a160 bedded, not-for-profit, community hospital, located in Dhulikhel, 30 kms east of Kathmandu and provides health services to Kavreplanchowk and other surrounding districts. It has got various clinical departments like Medicine, Cardiology, Surgery, Pediatrics, Orthopedics, Dental etc. On an average 150-200 patients visit the out-patient (OPD) of hospital daily.

2. Saheed Gangalal National Heart Center, Kathmandu (SGNHC): It is a 62 bedded specialized hospital located at Bansbari, Kathmandu. It is the only one hospital in Nepal where open heart surgery is performed. It has got various units like Critical care unit, Intensive care unit, Emergency and the OPD. On an average nearly 200-250 patients visit hospital everyday.

Study type: Prospective, observational study.

Study duration: Eleven months (Sep 2005 to July 2006).

Study population: Totally 72 patients were enrolled in this study. They were divided into two groups (36 in amlodipine and 36 in enalapril group).

Inclusion criteria: The inclusion criteria of this study were
1. Hypertensive patients diagnosed newly or diagnosed earlier but not taking medication for the past 2 weeks.
2. Patients in any age belonging to both sexes.
3. Patients in mono antihypertensive therapy either with amlodipine or enalapril at the beginning.

Exclusion criteria: Exclusion criteria of this study were
1. Patients suffering from secondary hypertension
2. Pregnant and nursing women
3. Patients prescribed with more than one antihypertensive drug
4. Patient taking drugs that can alter BP
5. Patients with known allergy to either amlodipine or enalapril.

Recording of BP: An average of two BP was taken in sitting position in both hands. The arm with the higher BP was taken into account. Following points were kept into consideration while taking measurement.
1. Properly maintained device was used
2. Patient was allowed to sit for at least 5 minutes in chair with feet on the floor and arm supported at heart level in a quiet room before beginning BP measurement
3. Tight clothing was removed, both arms were support at heart level and talking was avoided during procedure
4. Proper size cuff was used
5. The deflection rate of mercury column was maintained 2-3 mmHg/second
6. Measurements of BP in both arms typically were obtained.

Recording of pulse rate: Pulse rate was recorded manually by the researcher by palpating the radial artery over an underlying radial bone.

Operational modality: Permission was obtained from the institutional ethical committee of the study sites. Patient history was taken and patient meeting the inclusion criteria was taken for this study by taking written consent. Patient's BP and pulse rate prior to medication were recorded in the patient profile form. Patients were advised to take their medication at home and were followed after one week in out-patient department (OPD) and their BP and pulse rate were recorded again in the patient profile form. Patients were advised to continue their medication and were followed in OPD after 4 weeks. Patients BP and Pulse rate were again recorded in the patient profile form at 4 weeks. The ADR experienced by the study population were recorded in the patient profile form based on the patient complaints and patient interview.

Result analysis: All the information recorded in the patients profile forms were analysed for various parameters like age distribution, sex distribution, racial distribution, patients educational status, occupational status, habitat of patient, risk factor, dietary habit and patient complaints, mean reduction in BP and pulse rate and the ADRs experienced by the patients within the study period.

Statistical analysis: Statistical analysis in this study was carried out using SPSS version 11. Chi square ($\chi 2$) test and paired sample t-test were used for analyzing the data. P value of less than 0.05 was considered statistically significant.

Results

1. Patients demography: The demography detailed showed that more number of patients (20.83%) in this study was found in age group 31-40 years. The male patients were more (52.78%) in number. Newar race was more in number (44.44%). Nearly 60% of study population did not have their schooling education. Occupation wise 44.44% were found housewives. We found 58.33% of patients in this study were from the urban region and the most of the patients (91.67%) in this study were non-vegetarian. The details of patient's demography are given the table 1.

2. Risk Factors:
The smoking habit in both groups were equally distributed and there were not statistically significant difference (P = 0.846). Only less number of patients are found diabetic (4.17%). Over all we found that 26.39% of hypertensive patient have family history of hypertension. We found that 27.78% of hypertensive patients in this study had habit of taking alcohol and on interview it was found that most of them consumed alcohol occasionally in limited quantity. Our study demonstrated that 19.44% of patients were taking more salt. The physical activity in both groups were equally distributed and there was not statistically significant difference (P = 0.465). Over all we found that only 5.6% of patients perform more activity. The details of risk factor associated with the patients are given in the table.2

3. Presenting complaints of the patients: Among all the patients 29.17% of patients knew their diagnosis and they did not have any complaints; they came for their routine check up. As described in the literature, most of the patients were asymptomatic and only few patients were presented with the specific symptoms like headache, palpitation and dizziness.

4. BP of the patients during study period: The mean reductions in the BP during the period of this study are shown in figure 1 and 2.

5. Pulse rate (PR) of the patients during study period: The detail in pulse rate reduction is shown in figure 3.

6. Adverse effects profiles of study patients: The detailed adverse effect profiles of the both drugs are given in the table 3.

Table 1. Patient demography

Description	Category	Amlodipine (n=36)	Enalapril (n=36)	Total (n=72)
Age	21-30	6 (16.67%)	5 (13.89%)	11 (15.28%)
	31-40	9 (25%)	6 (16.67%)	15 (20.83%)
	41-50	8 (22.22%)	6 (16.67%)	14 (19.44%)
	51-60	7 (19.44%)	6 (16.67%)	13 (18.06%)
	61-70	4 (11.11%)	9 (25%)	13 (18.06%)
	>70	2 (5.56%)	4 (11.11%)	6 (8.33%)
Sex	Male	21 (58.33%)	17 (47.22%)	38 (52.78%)
	Female	15 (41.67%)	19 (52.78%)	34 (47.22%)
Races	Brahmin	9 (25%)	7 (19.44%)	16 (22.22%)
	Chhetri	3 (8.33%)	2 (2.78%)	5 (6.94%)
	Newar	12 (33.33)	20 (55.56%)	32 (44.44%)
	Mongolian	8 (22.22%)	4 (11.11%)	12 (16.67%)
	Others	4 (11.11%)	3 (8.33%)	7 (9.72%)
Education	Schooling	17 (47.22%)	12 (33.33%)	29 (40.28%)
	Non schooling	19 (52.78%)	24 66.67%)	43 (59.72)
Occupational	Service	7 (19.44%)	4 (11.11%)	11 (15.28%)
	Business	7 (19.44%)	3 (8.33%)	10 (13.89%)
	Teacher	1 (2.78%)	3 (8.33%)	4 (5.56%)
	Farmer	4 (11.11%)	7 (19.44%)	11 (15.28%)
	Housewife	14 (38.89%)	18 (50%)	32 (44.44%)
	Others	3 (8.33%)	1 (2.78%)	4 (5.56%)
Habitat	Rural	15 (41.67%)	15 (41.67%)	30 (41.67%)
	Urban	21 (58.33%)	21 (58.33%)	42 (58.33%)
Dietary Habit	Vegetarian	3 (8.33%)	3 (8.33%)	6 (8.33%)
	Non- vegetarian	33 (91.67%)	33 (91.67%)	66 (91.67)

Table 2. Risk factors associated with the patients

Description	Category	Amlodipine (n=36)	Enalapril (n=36)	Total (n=72)
Smoking	Smoker	8 (22.22%)	10 (27.78%)	18 (25%)
	Past Smoker	9 (25%)	9 (25%)	18 (25%)
	Non-smoker	19 (52.78%)	17 (47.22%)	36 (50%)
Diabetic history	Yes	0 (0%)	3 (8.33 %)	3 (4.17%)
	No	36 (100%)	33 (91.67%)	69 (95.83)
Family history of hypertension	Yes	12 (33.33%)	7 (19.44)	19 (26.39%)
	No	24 (66.67%)	29 (80.56%)	53 (73.61)
Habit of taking alcohol	Yes	11 (30.56%)	9 (25%)	20 (27.78 %)
	No	25 (69.44%)	27 (75%)	52 (72.22)
Salt Intake	Mild	1 (2.78%)	5 (13.89%)	6 (8.33%)
	Moderate	28 (77.89%)	24 (66.67%)	52 (72.22%)
	More	7 (19.44%)	7 (19.44%)	14 (19.44%)
Physical activity	None	8 (22.22%)	12 (33.33%)	20 (27.77%)
	Mild	19 (52.77%)	15 (41.66%)	34 (47.22%)
	Moderate	6 (16.66%)	8 (22.22%)	14 (19.44%)
	More	3 (8.33%)	1 (2.77%)	4 (5.55%)

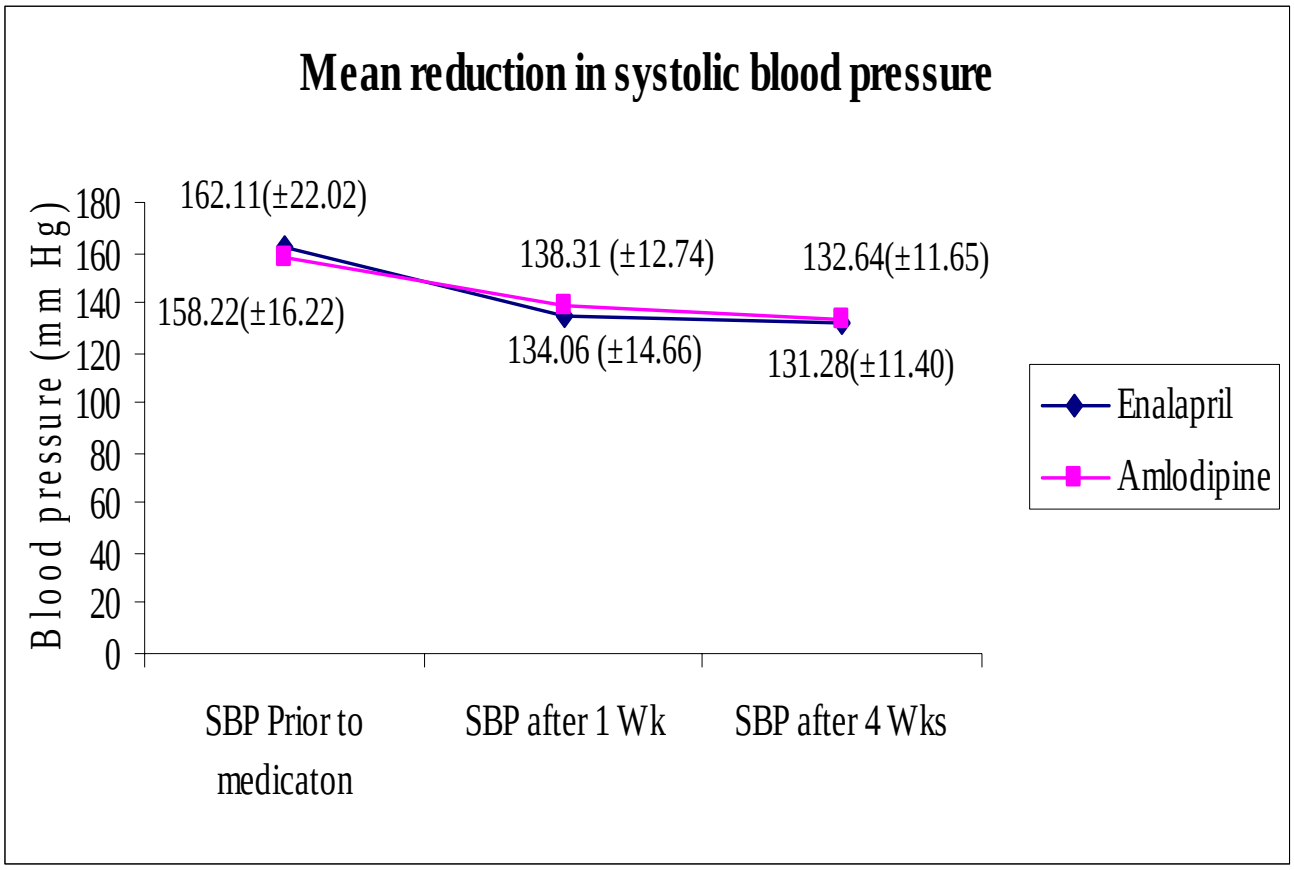

Figure 1. Mean reduction in systolic blood pressure

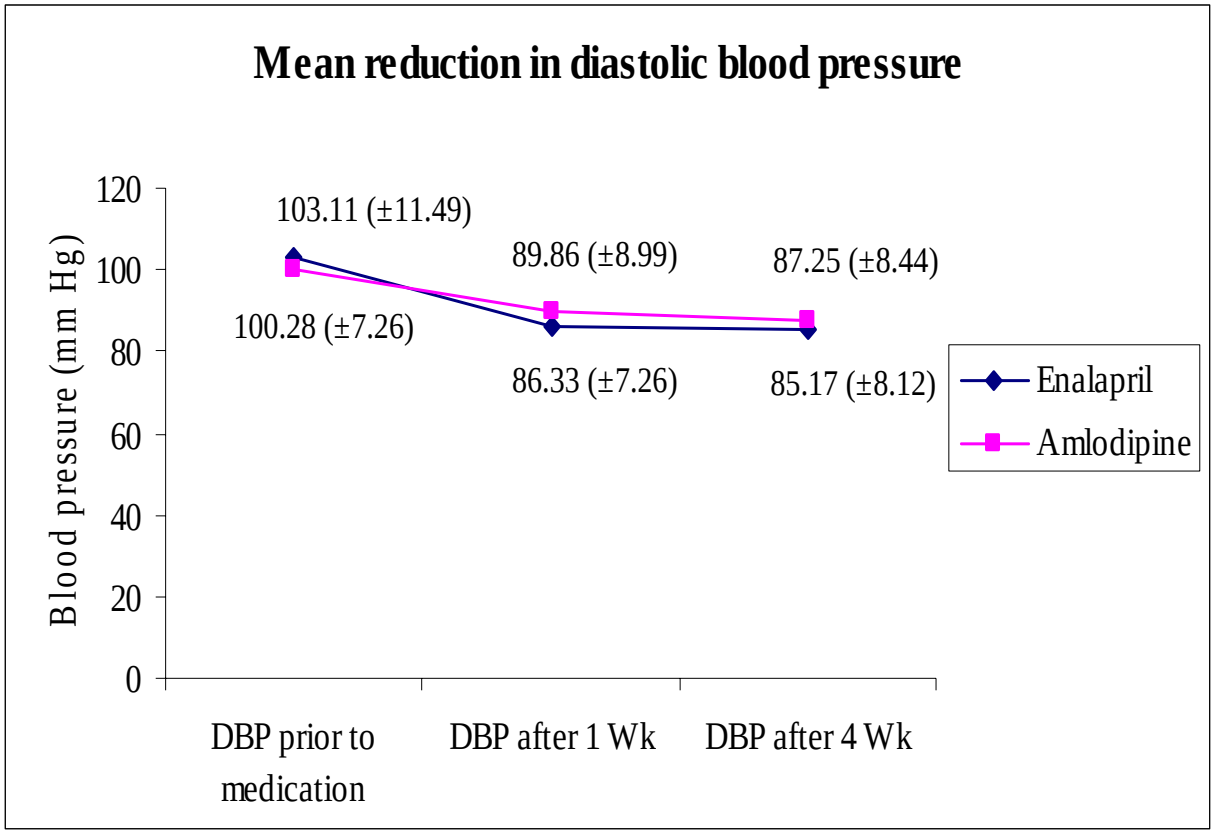

Figure 2. Mean reduction in diastolic blood pressure

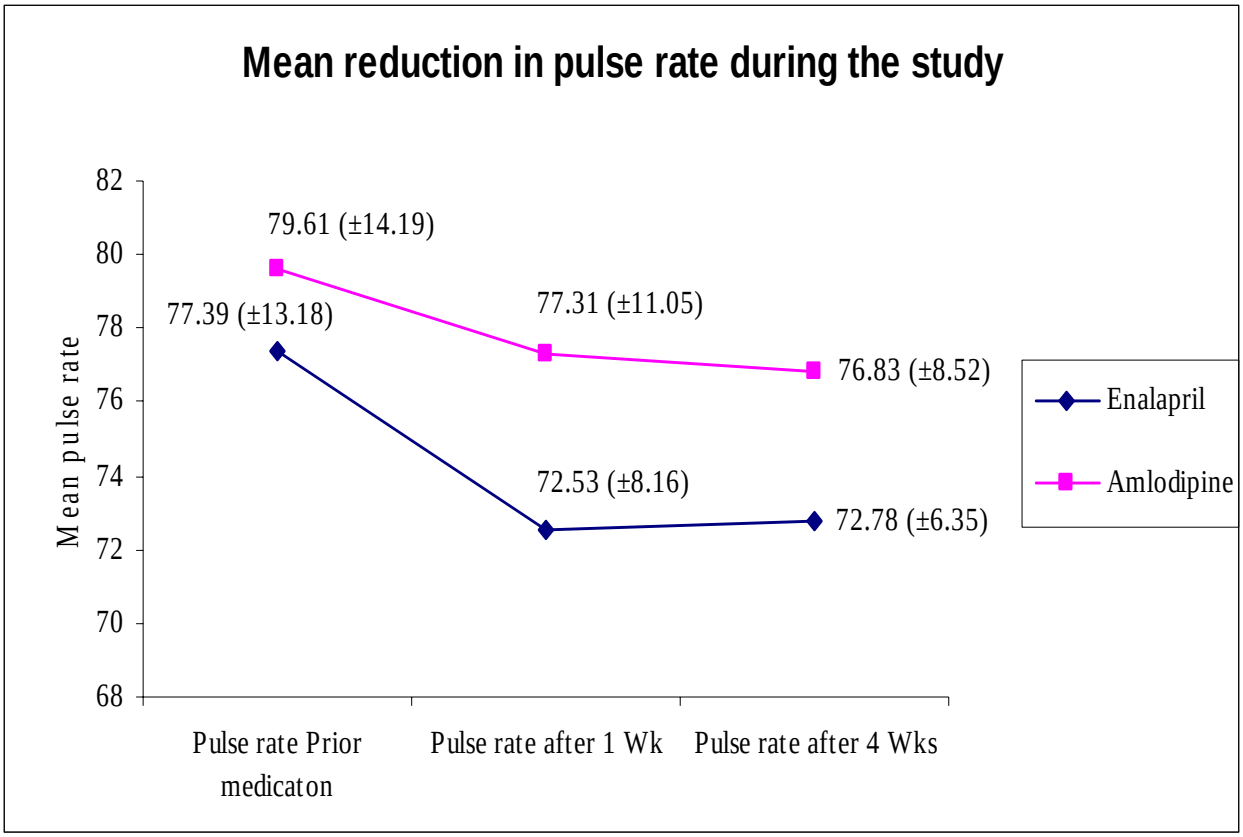

Figure 3. Mean reduction in pulse rate

Table 3. Adverse effects of study patients

S. No.	Amlodipine (n=37)	Enalapril (n=33)	Total (n=70)
Peripheral edema	4 (10.81%)	0	4 (5.71%)
Shortness of breath	4 (10.81%)	0	4 (5.71%)
Headache	8 (21.62%)	2 (6.06%)	10 (14.29)
Nausea	4 (10.81%)	5 (15.15%)	9 (12.86%)
Palpitation	2 (5.41%)	0	2 (2.86%)
Fatigue	3 (8.11%)	2 (6.06%)	5 (7.14%)
Weakness	1 (2.70%)	0	1 (1.43%)
Dizziness	2 (5.41%)	3 (9.09%)	5 (7.14%)
Flushing	2 (5.41%)	0	2 (2.86%)
Muscle cramp	1 (2.70%)	0	1 (1.43%)
Back pain	1 (2.70%)	0	1 (1.43%)
Abdomen pain	1 (2.70%)	0	1 (1.43%)
Water brash	1 (2.70%)	0	1 (1.43%)
Heavy headedness	1 (2.70%)	0	1 (1.43%)
Tingling sensation	1 (2.70%)	0	1 (1.43%)
Dry cough	0	7 (21.21%)	7 (10%)
Sinusitis	0	1 (3.03%)	1 (1.43%)
Rhinitis	0	1 (3.03%)	1 (1.43%)
Sore throat	0	3 (9.09%)	3 (4.29%)
Taste alteration	0	2 (6.06%)	2 (2.86%)
Vomiting	0	1 (3.03%)	1 (1.43%)
Chest pain	0	2 (6.06%)	2 (2.86%)
Decreased sleep	1 (2.70%)	2 (6.06%)	3 (4.29%)
Constipation	0	1 (3.03%)	1 (1.43%)
Anorexia	0	1 (3.03%)	1 (1.43%)

Discussion

The demographic details of the patients in both groups are similar. The risk factors in both of the groups was equally distributed Enalapril decreased systolic / diastolic BP from the initial mean BP 162.11 (±22.02)/ 103.11 (±11.49) mm Hg to 134.06 (±14.66) / 86.33 (±8.77) after 1 week, and reduced to 131.28 (±11.40) / 85.17(±8.12) mm Hg after 4 weeks which. Similarly, amlodipine reduced systolic / diastolic BP from 158.22 (±16.22) / 100.28 (±7.26) mm Hg to 138.31 (±12.74) / 89.86 (±8.99) after 1 week, and to 132.64 (±11.65) / 87.25 (±8.44) mm Hg after 4 weeks. Enalapril decreased the pulse rate from 77.39 (±13.18) to72.53 (±8.16) beats per minute (bpm) and to 72.78 (±6.35) bpm after 4 weeks. Similarly, amlodipine decreased pulse rate from 79.61 (±14.19) to 77.31 (±11.05) after 1 week and to 76.83 (±8.52) bpm after 4 weeks. Dry cough, nausea and dizziness with enalapril and headache, peripheral edema, nausea and shortness of breath with amlodipine were the common ADR.

Although, the assessment of the risk factor is not an objective of the study, it was made totally based on the patient interview. In this study, the impact from the non-pharmacological treatment was not considered. However, methodology in the study was followed properly.

The mean reduction in systolic / diastolic BP by enalapril after 1 week was statistically significant (P = 0.000, 0.000) and reduced after 4 weeks was not statistically significant (P= .131, 0.271). Similarly, the mean reduction in systolic / diastolic BP by amlodipine after 1 week was statistically significant (P = 0.000, 0.000) and reduced after 4 weeks was also statistically significant (P = 0.000, 0.008). The reduction in systolic and diastolic BP were more in enalapril group than the amlodipine group but was not statistically significant (P = 0.618, 0.289). The mean reduction in the BP in this study by individual drugs were more than the study conducted by *Gryglas P* [11] in Poland and *Fowler et al*. [12] in Denmark. This may be because of difference in ethnicity and culture of the study population. Although the above studies were similar to our study, in respect to doses it differed in terms of duration, they followed the patient for 8 weeks in comparison to 4 weeks of follow up in our study. We also found that enalapril reduces BP slightly more than amlodipine but was not significant statistically. This justifying that amlodipine and enalapril are equally effective in reducing the BP. This is similar to the study conducted by *Gryglas P* [11] and *Fowler et al*. [12] but the just opposite in the sense that amlodipine reduces slightly more BP than the enalapril. Again this is due to the difference in ethnicity and culture of the study population. We also found that reduction in BP after 4 weeks is statistically significant with amlodipine but not with enalapril indicating that amlodipine reduces the BP gradually.

Enalapril decreased the pulse rate from 77.39 (±13.18) to72.53 (±8.16) beats per minute (bpm) which was statistically significant (P = 0.004) and to 72.78 (±6.35) bpm after 4 weeks, which was not significant statistically (P = .803). Similarly, amlodipine decreased pulse rate from 79.61 (±14.19) to 77.31 (±11.05) after 1 week and to 76.83 (±8.52) bpm after 4 weeks which was not statistically significant (P = 0.071, 0.556). The reduction in pulse rate was found to be more in enalapril than amlodipine and the reduction was statistically significant (P = 0.041, 0.025). Similar results were found in *Frishman et al* [13] study in respect to the amlodipine. However, the reduction in pulse rate due to enalapril was significant and more than that of amlodipine.

We found that number of adverse effects experienced by the patients on amlodipine were more than the patient on enalapril, which is different to finding of *Gryglas P* study [11] where more adverse effects were experienced in enalapril group. Dry cough, nausea and dizziness were the main side effect

of the enalapril. However, headache, peripheral edema, nausea and shortness of breath were the major complaints of the patients in amlodipine which were similar to the *Fowler et al*. [12] study.
But the change in therapy was not required in the enalapril group where as two patient required changes in therapy in amlodipine group due to intense peripheral ankle edema, a finding differing from the *Omvik et al*. study [14] where equal number of patients were withdrawn from the therapy due to adverse effect. However, our study differs from the *Omvik et al*. with respect to comparative effect where they compared the quality of life of patients but we compared the anti-hypertensive effect.

Few limitations of our study are less number of patients, so we could not able to perform multiple regression analysis. Patients were followed only for 4 weeks and impact of non-pharmacological treatment in this study was not taken into account.

Conclusion

Our study concluded that both the study drugs (amlodipine and enalapril) were equally effective in terms of BP reduction. However, in terms of the pulse rate reduction and adverse reaction enalapril is more effective and safer than the amlodipine. As ankle edema was the major problem with the amlodipine which require change in therapy in two patients in our study. We recommend prescribers to monitor the patients on amlodipine for such adverse effects and counsel them about such adverse effects to improve the compliance. However, further studies in large number of patients covering different regions of Nepal are needed to extrapolate these findings. We also recommend that the design of such study should include effects from the non-pharmacological treatment and patients should be followed for longer time to obtain the long term effects of drugs in terms of safety and efficacy.

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