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ANKLE EDEMA FORMATION DURING TREATMENT WITH THE AMLODIPINE IN A TERTIARY CARE HOSPITAL OF NEPAL

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ABSTRACT: Hypertension is one of the major public health challenges worldwide. Amlodipine, a calcium channel blockers (CCBs), is among the first line antihypertensive drugs used commonly. Amlodipine reduces blood pressure by its vasodilatory action and its adverse drug reactions (ADRs) such as ankle edema, headache and flushing are related with its vasodilatory action. This study is conducted to find the incidence of ankle edema in patients of mild to moderate hypertension treated with Amlodipine 10 mg. A total of 64 informed consented patients, fulfilling inclusion and exclusion criteria were involved in the study. Follow-up visits were performed after four weeks and eight weeks. At each visit, complete clinical examination was carried out, including a recording of systolic and diastolic blood pressure (BP). Safety was assessed in terms of both subjective and objective systemic adverse-effects. In the present study, significant reduction of mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) was seen. Commonly seen adverse drug reactions (ADRs) were ankle edema, constipation, headache and fatigue. The association of ankle edema due to amlodipine has alerted us to begin generating safety data of drugs on our own population.

INTRODUCTION: Hypertension is one of the most common diseases affecting human 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 in the form of myocardial infarction and stroke. ^{1, 2, 3} About half of the world's cardiovascular burden is predicted to occur in Asia Pacific region. ⁴

Despite all benefits demonstrated in response to blood pressure lowering, hypertension management remains suboptimal. ^{1, 5} The reasons have been repeatedly analysed ², among which the side-effects of antihypertensive drugs emerge as an important issue in clinical practice. 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. ⁶ Prevalence of hypertension in Nepal was estimated to be 27.8% of adults aged 25 years and above. ⁷

There are many drugs used in treatments of hypertension which includes angiotensin converting enzyme (ACE) inhibitors, beta blockers (BBs), calcium channel blockers (CCBs), diuretics, alpha blockers, angiotensin II receptor blockers,

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central alpha-2 agonists, adrenergic inhibitors, and vasodilators. Dihydropyridine calcium-channel blockers (CCBs) are one of the commonly used potent antihypertensive drugs and their vasodilatory effects are associated with adverse drug reactions (ADRs) such as ankle edema, headache and flushing.⁸ Ankle oedema is a dose related common adverse event observed during treatment with CCBs. In many cases, ankle oedema is responsible for treatment discontinuation or limited patient's compliance to anti-hypertensive treatment and has a deleterious impact on health-related quality of life.⁹ The objective of the study is to find the incidence of ankle oedema in the patients treated with CCBs.

MATERIAL AND METHODS: This was a prospective observational non interventional study conducted in the out-patient department (OPD) of internal medicine in a tertiary care center; Chitwan medical college and teaching hospital, Nepal. Approval from the institutional ethics committee was obtained to conduct the study. Male and female patients, aged 18-75 years, newly diagnosed with mild to moderate essential hypertension (systolic BP \geq 140 to 179 mmHg and/or Diastolic BP \geq 90 to 109 mmHg) were eligible for the study after obtaining informed consent. Patients with secondary hypertension, pregnant and lactating women, patient with other diseases and who need more than one antihypertensive drug are not included in the study. Total 72 patients were included in study but only 64 patients completed the study.

Each enrolled patient was subjected to the detailed medical history, demography and physical examination. Measurements of systolic and diastolic BP were performed manually with a calibrated mercury sphygmomanometer in sitting position. Follow-up visits were performed after four weeks and eight weeks. At each visit, complete clinical examination was carried out, including a recording of systolic and diastolic blood pressure (BP). Safety was assessed in terms of both subjective and objective systemic adverse-effects. The degree of ankle edema on physical examination was visually scored by the physician on a scale ranging from 0 to 3 (0 = none, 1 = mild, 2 = moderate or 3 = severe, respectively), taking

into account the changes of edema that occurred from visit to visit.

RESULTS: Among the 72 patients of mild to moderate hypertension, the data of 70 patients were considered for the study. Two patients were lost to first follow-up after enrollment and four patients' data was excluded due to major protocol violation. Thus, only 64 patients completed the study. In this study, it was found that 57.8% patients were male and 42.2% were female. Thus the distribution of patients, according to sex, was not significantly different ($P = 0.211$). Details of age distribution, personal habits of patients are given in **Table 1** and **2**. Detail about educational status of patients are shown in **Fig.1**.

TABLE 1: AGE DISTRIBUTION OF PATIENTS

Age in years	N	%
<40	4	6.3
40-50	14	21.9
50-60	24	37.5
> 60	22	34.4
Total	64	100

TABLE 2: DETAILS OF PATIENT'S HABITANTS

	N (%)
Food habit	Vegetarian 52 (81%)
	Non-vegetarian 12 (19%)
Smoking habits	Yes 33 (51%)
	No 31 (66%)
Alcohol consumption	Yes 23 (36%)
	No 41 (64%)
Family history	Yes 27 (42%)
	No 37 (58%)

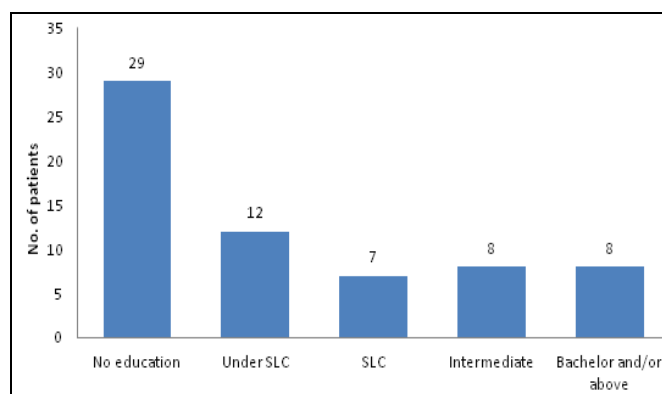


FIG. 1: THE DETAILS OF EDUCATIONAL STATUS OF PATIENTS

In this study reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to end of study visit was statistically highly significant (p value <0.001) (**Table 3**).

TABLE 3: TEST OF SIGNIFICANCE IN MEAN REDUCTION IN BP TREATED WITH AMLODIPINE 10 MG

Blood pressure category	Mean BP (before)	Mean BP (after)	Mean difference	P value
SBP* Prior medication to four week	157.6±7.7	139.7±6.6	17.9	0.000
DBP* Prior medication to four week	96.2±5.2	85.8±4.9	10.4	0.000
SBP four week to eight weeks	139.7±6.6	135.5±6.0	3.75	0.000
DBP one week to eight weeks	85.8±4.9	84.8±4.9	0.8	0.023
SBP prior medication to eight weeks	157.6±7.7	135.5±6.0	20.0	0.000
DBP prior medication to eight weeks	96.2±5.2	84.8±4.9	10.8	0.000

*SBP: Systolic BP, *DBP: Diastolic BP

Adverse drug events, considered to be related to the study drug, were infrequent. Apart from ankle edema, in total 25 (39%) patients complains of adverse drug reactions (ADR) which includes ankle edema, headache, dizziness and nausea. (Table 4) Out of 15 ankle edema eight have mild, six have moderate and one has severe edema which is highly significant (P=0.000).

TABLE 4: DISTRIBUTION OF ADRs

Types of ADR	No.	Percent
Ankle edema	15	23.4
Headache	12	18.7
Dizziness	10	15.6
Nausea	10	15.6
Constipation	9	14.1
Fatigue	8	1.2

DISCUSSION: In this study, it was found that 57.8% patients were male and 42.2% were female. The distribution of patient according sex was different from distribution found by Oguri *et al.*,¹⁰ at Japan. Most of the patients were non-educated. This may be because majority of the patients were from rural area and they were less conscious about their health.

The food habit of the patient was categorized as vegetarian and non vegetarian. Among them, majority of the patients were nonvegetarian (81.3%). The distribution of patients was significantly different according to food habit (P = 0.000) and it is similar to the findings of Alam *et al.*,¹¹ The reason of developing hypertension in non-vegetarian person might be the high content of saturated fat, carbohydrate and less percentage of fiber in non vegetarian food and all these factors have positive effect on developing high blood pressure.^{12, 13}

Most of the patients were found to be smoker (51.6%). The distributions of smokers and non – smokers patients was not significantly different (P = 0.803) though smoking is one of the major risk

factor for hypertension.¹⁴ The reason of such result might be because of the small sample size taken for the study.

In total it was found that 57.8% of patients had no family history of hypertension. The occurrences of hypertension in the patients with or without family history was not significantly different (P=0.211). A study in Nepal also found that 73.61% of hypertensive patients had no family history of hypertension.¹¹ The reason of such result might be because of the fact that patients were unaware of the BP status of their family. In this study 64.1% of total patients did not consume alcohol and the result of the study is similar to the study conducted by Alam *et al.*, in Nepal¹¹ but different from the result of Xin *et al.*,¹⁵ and Joshi *et al.*,¹⁶ The occurrence of hypertension in non alcoholic group was significantly higher than in non alcoholic (P = 0.024).

The mean percentage decrease in systolic/diastolic blood pressure after four week and eight week was highly statistically significant (P = 0.000, 0.000). This result is similar to the study conducted in Nepal¹¹ Poland¹⁷ Denmark¹⁸ and China.¹⁹

The present study demonstrated that, significantly higher total AEs in general, and ankle edema in particular in the long-term management of mild to moderate hypertension. The incidence of ankle edema formation in our study is 23.4% which is similar to the study Lombardo D *et al.*, 1994 (23%)^{20, 21} and lower than the study conducted by Andresdottir MB *et al.*,²² (47%) and Per Lund-Johansen *et al.*,²³ (33.3%) Although dihydropyridine amlodipine are powerful antihypertensive agents, their vasodilatory effects are associated with AEs such as ankle edema, headache and flushing.⁸ It is generally accepted that in response to blood pressure lowering after amlodipine, the baroreflex-induced activation of the sympathetic system leads to contraction of

postcapillary venules, which in turn increases the pressure gradient at the capillary level. Hydrostatic pressure aggravates the phenomenon of capillary transudation.⁹

In the meantime, pre-capillary arteriolodilatation, a direct effect of dihydropyridines, protects against the vasoconstrictive effects of sympathetic activation.^{9, 24, 25}

CONCLUSION: The association of ankle edema due to amlodipine has alerted us to begin generating safety data of drugs in our own population, rather than relying on the data generated from the foreign population, which may vary significantly with regard to genetic make-up, diet, lifestyle etc. Clinicians have a responsibility to monitor the patients on drugs like amlodipine. Since our observations are based on only 64 cases, there is a need for more data to confirm our findings.

REFERENCES:

- Jones LD, Adams R, Carnethon M, Simone G, Ferguson TB, Flegal K, *et al.*; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics – 2009 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008; 119: e1 – e161.
- Mancia G, Backer G, Cifkova R, Dominiczak A, Fagard R, Germano G, *et al.*, Guidelines for the Management of Arterial Hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Cardiology (ESC) and of the European Society of Hypertension (ESH). *J Hypertens*. 2007; 25:1105–87.
- Ezzati M, Lopez AD, Rodgers A, Horn VS, Murray CJL, The Comparative Risk Assessment Collaborative Group. *Lancet*. 2002; 360:1347–60.
- Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S; Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in Asia Pacific region. *J Hypertens* 2003; 21: 707-16.
- Bramlage P, Thoenes M, Kirch W, Lenfant C. Clinical practice and recent recommendations in hypertension management-reporting a gap in a global survey of 1259 primary care physicians in 17 countries. *Curr Med Res Opin*. 2007; 23: 783-91.
- World Health Report 2002: Reducing risks, Promoting healthy life. Geneva, Switzerland: World Health Organization. 2002. (<http://www.who.int/whr/2002/>)
- World Health Organization. Global health observatory. Geneva. <http://apps.who.int/gho/data/?theme=main#> - accessed 22 March 2013.
- Opie LH. Calcium channel antagonists. Part IV: Side effects and contraindications drug interactions and combinations. *Cardiovasc Drugs Ther*. 1988; 2:177-89.
- Fogari R. Ankle oedema and sympathetic activation. *Drugs*. 2005; 65:S2:21-7.
- Oguri M *et al.*, Comparative effects of Enalapril versus Losartan on the prevention of diabetic nephropathy in type 2 diabetes patients with microalbuminuria *International Journal of Diabetes and metabolism*. 2009; 17:1-4.
- Alam K, Khan GM, Koju R, Thapa P. Comparative study on anti-hypertensive effects of amlodipine and enalapril in primary hypertension. *Pharmacologyonline* 2007; 1: 516-28.
- Melby CL, David G, Hyner GC, Lyle RM. Relation between vegetarian and nonvegetarian diets and blood pressure in black and white adults. *AJPH* 1989; 79(9): 1283-8.
- Toohy ML, Cebic K, Melby CL. Blood pressure and blood lipids among vegetarian, semi vegetarian and non vegetarian African, American. *Am jclini nutr* 1994; 59: 103-9.
- Donald G, Vidt *et al.*, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003; 251:2560-72.
- Xin X, He J, Frontini MG, Ogden LG, Motasamai OI, Whelton PK. Effects of alcohol on blood pressure. A meta-analysis of randomized controlled trials. *Hypertension*. 2001; 38:1112-27.
- Joshi M, Rao BS, Khan GM. Study of drug use in essential hypertension and their compliance Kathmandu university journal of science, engineering and technology 2006; 1:1-13.
- Gryglas P. The comparison of hypotensive efficiency and tolerability of amlodipine and enalapril in patients with essential hypertension. *Pol Arch Med Wewn* 2001; 105(2): 109-15.
- Fowler G, Webster J, Lyons D *et al.*, A comparison of amlodipine with enalapril in treatment of moderate/severe hypertension. *Br J Clin Pharmacol* 1993; 35 (5): 491-8.
- Dayi H D, Liu L, Li W. Efficacy and Safety of Valsartan/Amlodipine Single-Pill Combination in 11,422 Chinese Patients with Hypertension: an Observational Study *Adv Ther* (2014) 31:762–75.
- Andresdottir M, van Hamersvelt H, van Helden M *et al.*, Ankle edema formation during treatment with the calcium channel blockers lacidipine and amlodipine: A single-centre study. *Journal of Cardiovascular Pharmacology*. 2000; 35: S25-S30
- Lombardo D, Raimondi F. Efficacy and safety evaluation of lacidipine compared with amlodipine in mild to moderate hypertensive patients. *J Cardiovasc Pharmacol*. 1994; 23(S5): S98-100.
- Andresdottir M, van Hamersvelt H, van Helden M *et al.*, Ankle edema formation during treatment with the calcium channel blockers lacidipine and amlodipine: A single-centre study. *Journal of Cardiovascular Pharmacology*. 2000; 35: S25-S30
- Lund-Johansen P, Stranden E, Helberg S *et al.*, Quantification of leg oedema in post-menopausal hypertensive patients treated with lercanidipine or amlodipine. *Journal of Hypertension*. 2002; 1003-10.
- Fogari R, Zoppi A, Corradi L, Preti P, Malalamani GD, Mugellini A. Effects of different dihydropyridine calcium antagonists on plasma norepinephrine in essential hypertension. *J Hypertens*. 2000; 18:1871-5.
- Fogari R, Malamani GD, Zoppi A, Mugellini A, Viscardi A, Lastoria C, *et al.*, Manidipine has less oedematogeneous potential than amlodipine [abstract]. *J Hypertens*. 2000; 18 Suppl 2:S154-5.

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