

EVALUATION OF CAUSATIVE FACTORS IN AMLODIPINE INDUCED PEDAL EDEMA

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ABSTRACT

Objective: To study the edema causing factors in hypertensive, amlodipine-induced pedal edema patients.

Methods: The present was a prospective, observational study. A total of one hundred and twenty-four essential hypertensive patients, of either gender attending the outpatient department of cardiology and medicine, were recruited for this study. Out of the 124 patients, 62 were of the amlodipine-induced pedal edema [AIPE] group and other 62 patients were amlodipine-treated non-edema [ATNE] group. All the patients were receiving a dosage of amlodipine 5 mg/day. All recruited patients completed the study. The present study conducted at Kasturba Hospital, Manipal.

Results: The vanillyl mandelic acid (VMA) (mean±SD) 7.08±2.3 mg/24 h and 4.9±1.7 mg/24 h in AIPE and ATNE groups respectively. Blood pressure (BP) and VMA was higher in AIPE group than the ATNE group (p<0.001). Pulse rate (PR), serum proteins, creatinine, sodium, osmolality, did not show any significant difference between the two study groups.

Conclusion: In essential hypertensive patients with AIPE group presented with a higher VMA level than the ATNE group. The elevated catecholamine's possibly the causative factor for AIPE.

Keywords: Calcium channel blocker, Amlodipine, Pedal edema, Causative factors

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INTRODUCTION

Hypertension (HTN) is a major global health impact. The global burden of HTN is extremely high and globally one billion people are affected by HTN and in India; it has reached to 29.8% HTN is most common risk factors for cardiovascular, cerebrovascular and renal diseases [1, 2]. In most instances, it is asymptomatic, until and unless it affects the major organs like heart, kidney, cerebrovascular, peripheral vascular system including the eye. Early detection and treatment will reduce the risk and improves patient's quality of life [3-5].

According to Joint National Committee eighth report (JNC-8), in a general population, the antihypertensive drug therapy should be started when BP is ≥150/90 mm Hg in adult's ≥60 y. In patients ≤ 60 y, initiate the therapy and targeted goals should be ≤140/90 mm Hg, the same recommendation remains for the patient's age ≥18 y with either chronic kidney disease (CKD) or diabetes. The initial antihypertensive treatment regimen should be a thiazide diuretic, Calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), in the white population; initial therapy should be a thiazide-type diuretic or CCBs in a black population [6].

BP can be controlled by lifestyle modifications or with antihypertensive agents or both. The current pharmacological options to treat HTN include diuretics, CCBs, ACEIs, ARBs, sympatholytic drugs and vasodilators. The choice of drug therapy will be determined by the severity of diseases and associated patient factors [1, 7].

CCBs acts on voltage-dependent Ca⁺⁺ channels. The subtype includes L-type, N-type, T-type, P/Q-type and N-type, and they are widely spread throughout the body and play a crucial role in the maintenance of vascular tone [8]. Amlodipine is a third generation dihydropyridine group of CCB. Amlodipine is a very potent and long acting drug and also a well-tolerated antihypertensive agent. Ankle edema is one of the most common and frequent adverse effects of amlodipine. Peripheral edema is uncomfortable, sometimes

intolerable and may lead to a decline in patient's quality of life [9, 10]. The incidence of pedal edema ranges from 1.7% to 63.3% [7]. Monotherapy showed a higher incidence of pedal edema than the combination therapy [8]. According to literature, about 9.3% of patients discontinue therapy because of its adverse effects. Overcoming this important issue is to stop amlodipine therapy and switch to another group of antihypertensives. Usually, diuretics will not be effective in the resolution of CCBs induced pedal edema [11].

Edema is a condition where free fluids accumulate in the interstitial space. The important mechanism involves, the increased capillary hydrostatic pressure, decreased plasma oncotic pressure; increased capillary permeability and obstruction of the lymphatic system. However, there are many mechanisms postulated for AIPE, the exact mechanism and causative factors of ankle edema by CCBs is not clearly understood [11, 12].

The purpose of this study was to evaluate the causative factors in amlodipine-induced pedal edema and to compare the clinical parameters and biochemical parameters in hypertensive AIPE and ATNE groups.

MATERIALS AND METHODS

Methods

The present was a prospective, observational study. A total of one hundred and twenty-four hypertensive patients of either gender attending the outpatient department of cardiology and medicine recruited for this study. The patient's information sheet was given to all patients and explained about the present study; consent received before the study commences. Out of the 124 patients, 62 were of AIPE group and other 62 patients were in ATNE group. All the patients were receiving a dosage of amlodipine 5 mg/day. All recruited patients completed the study. The study protocol was confirmed, and approval of the Institutional Ethics Committee (Approval no IEC 681/2013). The present study conducted at Kasturba Hospital, Manipal, Karnataka, India.

Inclusion criteria

Hypertensive patients of either gender [$>140/90$ mm Hg], currently receiving amlodipine more than six months as an antihypertensive therapy. The age limit was 18 to 70 y. For AIPE group patients should develop AIPE [with no other obvious cause], and for ATNE group all the inclusion criteria were same except, patients should not develop edema.

Exclusion criteria

We excluded the patients for following reasons, patients with major organ failure, endocrine abnormalities like Cushing's syndrome, hypothyroidism. Pregnant women and women on oral contraceptive pills, patients on other class of antihypertensive agents, non-steroidal anti-inflammatory drugs, and steroids, patients with lymphedema, pulmonary hypertension, secondary hypertension, patients with the varicose vein, venous insufficiency. Exclusion criteria are same for both the study groups.

Study procedure

In the present study, a total of 124 patients [$n = 124$] recruited who met the inclusion criteria. The consultant cardiologist examined the patients. The BP measured using standard mercury sphygmomanometer. Three consecutive readings of BP and PR noted at an interval of 10 min. Pedal edema was confirmed by clinical method over the medial malleolus of both legs. After initial screening,

demographic parameters, family history, clinical examination findings and biochemical parameters were also noted. All 124 patients who are on amlodipine 5 mg/day as an antihypertensive treatment and in that 62 patients are in AIPE group, and other 62 patients are in ATNE group.

Statistical analysis

Descriptive statistics (mean \pm SD, Median, IQR, and Percentage) provided for demographic variables. Categorical variables were compared using Chi-square test, and continuous variables compared using independent t-test. The Mann-Whitney test compared the skew variables. All the analysed by SPSS v 15, $p < 0.05$, was considered to be statistically significant.

RESULTS

It was a prospective, observational study. Hence, all 124 recruited patients completed the study. The patient demographic parameters compared in table no 1, the patient's age was found to be 57.4 ± 10.3 and 58.5 ± 8.5 y in AIPE and ATNE groups respectively. Weights of AIPE and ATNE groups were 64.9 ± 10.7 and 61.85 ± 9.3 kgs. respectively. The mean height of patients in AIPE and ATNE groups was 157.3 ± 10.3 and 159.3 ± 9.1 cms. respectively. BMI was 25 ± 2.7 in both the groups. Type 2 Diabetic Mellitus (DM) in AIPE group was 24 [38.7%], and ATNE group was 26 [41.9%]. Demographic parameters and all other aspects, compared between the groups, there was no significant difference between them.

Table 1: Comparison of demographic parameters of AIPE and ATNE groups

S. No.	Variables	AIPE [n=62] [mean \pm SD]	ATNE [n=62] [mean \pm SD]	P-VALUE*
1	Age [years]	57.4 \pm 10.3	58.5 \pm 8.5	0.53
2	Weight [Kgs]	61.85 \pm 9.3	64.9 \pm 10.7	0.28
3	Height [Cm]	157.3 \pm 10.3	159.3 \pm 9.1	0.25
4	BMI	25 \pm 2.7	25 \pm 2.7	0.34
5	T2 DM	24 [38.7%]	26 [41.9%]	0.86
6	Gender [M/F]	31/31 [50%/50%]	38/24 [61.3%/38.7%]	0.19

The values are expressed in mean \pm SD (%). Categorical variables were compared using Chi-square test; continuous variables are compared by independent t-test. * $P < 0.05$, was consider to be statistically significant.

Abbreviation

AIPE: Amlodipine induced pedal edema, ATNE: Amlodipine treated non edema BMI: Body mass index, DM: Diabetic mellitus, Kgs: Kilograms, Cm: Centimeters, M/F: Male/Female.

Table 2, Comparison of the clinical parameters between AIPE and ATNE groups. The systolic and diastolic blood pressure (SBP and DBP) showed a significant increase in AIPE group than the ATNE group. PR and LV ejection Fraction did not show any significant difference between the two study groups.

Table 2: Comparison of clinical parameters between AIPE and ATNE groups

S. No.	Variables	AIPE [n=62] [mean \pm SD]	ATNE [n=62] [mean \pm SD]	P-Value*
1	SBP [mmHg]	142.8 \pm 3.6	138.9 \pm 4.4	<0.001
2	DBP [mmHg]	83.65 \pm 4.6	80.24 \pm 4.4	<0.001
3	PR [B/M]	78 \pm 9	77 \pm 8	0.432
4	LV F [%]	65 \pm 5	65 \pm 3	0.375
5	IVC [mm]	15 \pm 1.5	15 \pm 1.5	0.150

The values expressed in mean \pm SD. Continuous variables compared by independent t-test. * $P < 0.05$. Is consider being statistically significant

Abbreviation

AIPE: Amlodipine induced pedal edema, ATNE: Amlodipine treated no edema, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR: Pulse rate, LVF: Left ventricular ejection fraction, IVC: Inferior vena cava, B/M: Beats/minutes, mm: Millimeters.

Table 3, Comparison of the biochemical parameters between AIPE and ATNE groups. VMA (mean \pm SD) 7.08 ± 2.3 mg/24 h and 4.9 ± 1.7 mg/24 h in AIPE and ATNE groups respectively. AIPE

group showed increased VMA of 2.18 mg/24 h, which is statistically significant. We put ROC curve for VMA, which covers 76.8% Area under the curve (AUC) with specificity 72.6% and sensitivity 71.2%. The cut-off value was 5.65 mg/24 h.

More than the VMA cutoff value patients have 6.4% higher chance to cause of AIPE. (Odds ratio was 6.4). We compared the other parameters are like total serum protein, albumin, globulin, creatinine, sodium, and osmolality, between the two groups. There was no significant difference seen between the two groups.

Table 3: Comparison of clinical parameters between AIPE and ATNE groups

S. No.	Variables	AIPE [n=62] [mean±SD]	ATNE [n=62] [mean±SD]	P-Value*
1.	Serum creatinine [mg/dL]	1±0.23	1±0.21	0.745
2.	Total protein [g/dL]	7.5±0.44	7.5±0.49	0.123
3.	Serum albumin [g/dL]	4.5±0.46	4.3±0.38	0.049
4.	Serum globulin [g/dL]	3.07±0.37	3.1±0.58	0.391
5.	Serum Na+[mmol/l]	139.5±3.21	138.8±3.38	0.233
6.	Serum osmolality [mosml/kg]	288.3±12.51	289.1±9.7	0.708
7.	VMA [mg/24 h]	7.08±2.3	4.9±1.7	<0.001

The values expressed in mean±SD. Continuous variables compared by independent t-test. *P<0.05 considered to be statistically significant

Abbreviation

AIPE: Amlodipine induced pedal edema, ATNE: Amlodipine treated no edema, VMA: Vanillyl mandelic acid

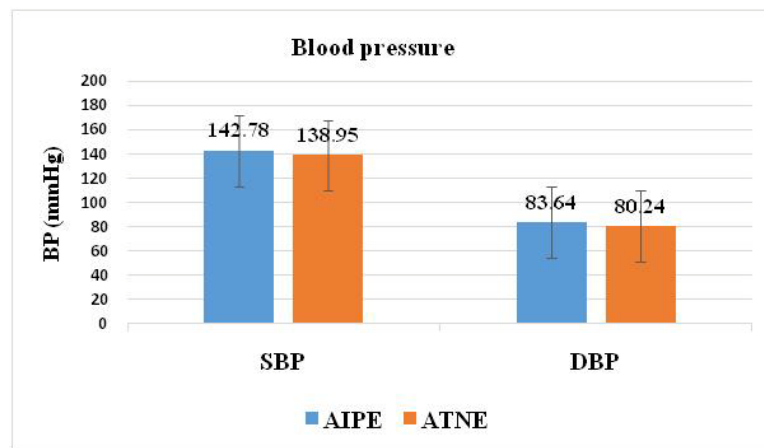


Fig. 1: Error diagram showing the comparison of SBP and DBP between AIPE and ATNE group (n=62 in each group). AIPE group showed significantly higher SBP and DBP than ATNE group (P<0.05)

Abbreviation

AIPE: Amlodipine induced pedal edema, ATNE: Amlodipine treated no edema, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

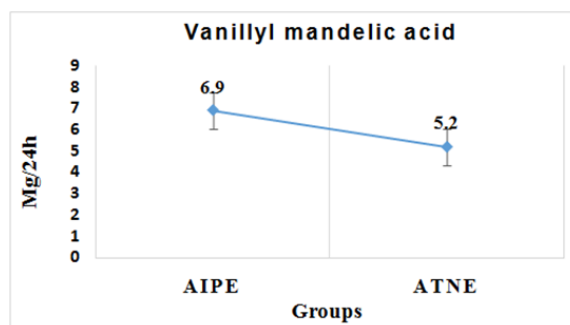


Fig. 2: Line diagram showing a comparison of vanillyl mandelic acid (VMA), between Amlodipine induced pedal edema group (AIPE) and amlodipine-treated non edema group (ATNE) (n=62 in each group). AIPE group showed significantly higher VMA level than the ATNE group (P<0.05)

DISCUSSION

Amlodipine is a third generation [13], dihydropyridine group of CCB, it is commonly used as an antihypertensive agent, because of its excellent pharmacological properties. The main drawback of this drug is which produces pedal edema in a wide range. AIPE patients show decreased the quality of life regarding self-care, mobility, pain, and discomfort. Edema causes more anxiety in hypertensive patients [14]. People who are suffering from anxiety were two to three times more likely to develop hypertension [15]. In our study, the BP was significantly higher in AIPE group than the

ATNE group, even though they are on same antihypertensive medication. Many studies have explained the direct relationship between hypertension and anxiety [16]. Pedal edema which causes psychosocial stress which associated with anxiety and which stimulates the autonomic nervous system (ANS), which leads to increase in circulating catecholamines [17]. There are many mechanisms postulated for AIPE, and the principal mechanism involves interference of normal autoregulatory postural vasoconstrictor reflexes [7]. Hydrostatic pressure and osmotic pressure plays a major role in the capillary fluid exchange. The imbalance between these two pressures leads to edema [18]. In the present study, we compared the plasma proteins between AIPE group and ATNE group, but there was no significant difference seen.

The antihypertensive effect of amlodipine is related to its mechanism of action. Amlodipine blocks the L-type calcium channels and relaxes the vascular smooth muscles. In contrast to arterioles, venules seem not to respond to L-type CCB [7]. The persistent increase in catecholamine levels after chronic treatment with amlodipine enhances the release of 50% more catecholamine than the normal [19, 20]. In our study, we found significantly higher 24 h. Urine VMA in AIPE group than ATNE group. VMA is ending metabolite of catecholamine [21]. The sympathetic stimulation or elevated plasma concentrations of catecholamine play a major role in edema [22].

Amlodipine inhibits the precapillary vasoconstriction through arteriolar dilatation [8]. However, amlodipine has less effect on venules; the increased catecholamine by chronic amlodipine therapy [19], which acts on adrenergic receptors on venules, which results in constriction of venules. So this produces the imbalance between the inflow and outflow between arterioles and venules. The difference in pressure gradient between arterioles and venules which possibly

producing pedal edema. From this study, we can predict that catecholamine plays a major role in amlodipine-induced pedal edema.

The solution to resolving the amlodipine-induced pedal edema is to stop the monotherapy of amlodipine and start with combination therapy or switching to L/N type of calcium channel blocker which will suppress catecholamine release from sympathetic nerves, and it helps in dilating both arterioles and venules, which may lead to the lesser incidence of edema.

Limitations

- The present study was an observational study. Hence, it was difficult to avoid or assess bias, and the conclusions are not always easily applicable across a generalize population.
- A urine sample (24 h.) collected for VMA test. We did not monitor the outpatient's food habits, water, and salt intake; it may interfere the VMA level.
- The few study patients travelled to our hospital from long distance with upright posture; it may vary the pedal edema size.

CONCLUSION

In essential hypertensive patients with AIPE group presented with a higher VMA level than the ATNE group. The elevated catecholamine's possibly the causative factor for AIPE.

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CONFLICT OF INTERESTS

Declared none

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