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Original Article

Efficacy and Tolerability of Amlodipine-Valsartan Compared to Amlodipine-Atenolol Combinations in Hypertensive Patients: A Prospective Comparative Study

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ABSTRACT

Amlodipine-valsartan and amlodipine-atenolol combination therapies may be used in patients where blood pressure is not adequately controlled on either component monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. Single-pill combinations of amlodipine-valsartan and amlodipine-atenolol are available in Bangladesh for the treatment of patients with hypertension. This trial was designed to determine the efficacy and tolerability of valsartan and atenolol when both were combined with the calcium channel blocker (CCB) amlodipine. Efficacy was assessed by the patient's blood pressure reading and tolerability based on the patient's complaints at each follow-up. This interventional, prospective, comparative study was conducted in the outpatient department (OPD) of cardiology in collaboration with the outpatient department of medicine of Sylhet M.A.G Osmani Medical College Hospital between January 2022 and October 2022. The study included 80 patients with essential hypertension resistant to 4 weeks of 5 mg of amlodipine. Blood pressure and pulse rate were measured at preinclusion, inclusion (One week), and after 4 weeks, 8 weeks and 12 weeks of active treatment with an amlodipine-valsartan combination (5/80 mg) and an amlodipine-atenolol combination (5/50 mg). From baseline to week 12, both systolic and diastolic blood pressure decreased significantly in the amlodipine-valsartan group (-21.82±0.17/ -16.82±1.78 mmHg; p<0.001) than the amlodipine-atenolol group (-14.15±0.03/ -6.82±0.47 mmHg; p<0.001). Pulse rate reduction was significant both in the case of amlodipine-valsartan group (-4.9±11.6; p<0.0001) and the amlodipine-atenolol group (-10.3±11.7; p<0.0001), but more reduction was observed in the amlodipine-atenolol group and was statistically significant (13.7% vs 3.9%; p<0.001). The amlodipine-valsartan combination decreased blood pressure more than the amlodipine-atenolol combination. However, in terms of pulse rate reduction, the amlodipine-atenolol combination was more effective.

Keywords: *Hypertension, Amlodipine, Valsartan, Atenolol.*

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INTRODUCTION

Hypertension (HTN) is one of the most prevalent health problems worldwide, associated with high morbidity and mortality. The global prevalence of hypertension has been noticeably increasing for the past two decades.

Worldwide, at least 1 billion people have hypertension, and a predictable figure of 1.5 billion is expected by 2025[1]. The prevalence of hypertension increases with age[2]. Hypertension is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg[3]. An estimated 77.9 million Americans have elevated blood pressure. Of these, 78% are aware of their diagnosis, but only 68% are receiving treatment, and only 64% of those treated are under control[4]. Data from the Framingham Cohort Study indicate that blood pressure has a sequential relationship with cardiovascular risk that significantly increases when systolic blood pressure rises >155 mmHg. Based on these data, it has been recommended that individuals with blood pressures of 120–139/80-89 mmHg should be categorized as having prehypertension[5].

Uncontrolled hypertension enhances target organ damage and significantly increases disease burden in the community. For this reason, aggressive control of hypertension is mandatory to protect public health in Bangladesh and worldwide. It is documented that monotherapy does not adequately control BP in up to 50% of patients[1,3,6,7]. That's why, most patients with hypertension need at least two antihypertensive agents to achieve blood pressure control. In light of the need to attain blood pressure goals, both the European Guidelines and the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) now suggest combination therapy, particularly when monotherapy fails to reach BP goals or in patients at high cardiovascular (CV) risk[7]. Combination therapy with antihypertensive agents exerts different mechanisms of action and is possibly responsible for a more effective decrease in blood pressure[8]. Meanwhile, fixed-dose combination therapy with different classes of drugs is increasingly used as an alternative[8]. Fixed combination therapy offers several advantages over monotherapy, and these include improved antihypertensive efficacy and reduced time required to attain BP targets. Fixed-dose combinations of two antihypertensive drugs in a single tablet are recommended because these combinations reduce inconveniences, improve adherence, and consequently increase the blood pressure control rate[9]. In addition, since lower doses of these agents are required to acquire the same efficacy, patients also experience fewer side effects[10]. Moreover, better levels of compliance are achieved due to the reduced number of tablets taken[10]. This is particularly important for patients with co-morbid conditions that require multiple medications. Presently, a wide range of fixed-dose combination antihypertensive therapies are available.

In the recent hypertension guidelines published by the American Society of Hypertension (ASH) and International Societies of Hypertension (ISH), which were endorsed by the Asia Pacific Society of Hypertension (APSH), only two antihypertensive dual combination treatments were recommended: rennin-angiotensin system (RAS) blockers plus either diuretic or calcium channel blockers (CCB)[11]. In the British hypertension guidelines from 2011, recommendations are similar, but preference is given to combining a RAS blocker with a CCB[12].

One of the most widely studied of such combinations is the ARB valsartan plus the CCB amlodipine. The efficacy and safety of that combination have been established in several randomised controlled trials. This combination also possibly counteracts the side effects of the other. For example, calcium antagonists are powerful, intrinsically natriuretic, and vasodilators, resulting in a negative sodium balance and the stimulation of the renin-angiotensin-aldosterone system (RAAS), while angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, in contrast, block the RAAS and, if administered in combination with calcium antagonists, in fact enhance their antihypertensive effects. Peripheral oedema, one of the side effects of dihydropyridine calcium antagonists, probably results from preferential arteriolar vasodilation and an increase in the pressure gradient between the arterial and venous capillaries, causing exudation of interstitial fluid[13]. This effect can be improved through concurrent administration of ARBs or ACE inhibitors, which reduce the precapillary resistance, normalise the intracapillary pressure and reduce fluid exudate[8]. In addition, suppression of the RAAS has been established to protect against target organ damage and reduce the risk of cardiovascular disease[14].

Amlodipine and atenolol are also commonly employed in the treatment of high blood pressure. Atenolol is a b_1-selective (Cardio-selective) beta-adrenergic receptor blocking agent that has cardioinhibitory, central sympatholytic, and renin-angiotensin axis inhibitory properties to reduce high blood pressure. The combination therapy with amlodipine and atenolol blocks the counter-regulatory responses that are

activated by the disturbance of the blood pressure regulatory mechanisms; for example, reflex tachycardia induced by amlodipine is mitigated by the negative chronotropic effects of atenolol. Some studies have shown that combining atenolol with amlodipine reduces the rate of constipation by up to 4 times as compared to amlodipine montherapy[15]. Clinical trials are ongoing to evaluate the efficacy and safety of amlodipine-valsartan and amlodipine-atenolol in various patient populations, the results of which are readily anticipated. But the data are lacking for the South Asian population. So, the present study was conducted to determine the efficacy and tolerability of amlodipine-valsartan and amlodipine-atenolol in hypertensive patients.

MATERIALS AND METHOD

This interventional, prospective, comparative study was conducted in the outpatient department of cardiology in collaboration with the outpatient department of medicine of Sylhet M.A.G. Osmani Medical College Hospital over a period of ten months between January 2022 and October 2022 after obtaining permission from the institutional ethical committee and written informed consent from the patients. Mild to moderate hypertensive patients (Daytime ambulatory blood pressure >135 and/or >85 mmHg) diagnosed newly or diagnosed earlier but not taking medication for the past 2 weeks, patients in mono antihypertensive therapy and being aged between 21 and 75 years were included in this study. After a 1-week washout period followed by a 4-week run-in period with amlodipine 5 mg (Once daily), patients still presenting uncontrolled blood pressure (Defined as SBP 140 mmHg or DBP >90 mmHg) were selected. Exclusion criteria included the following: blood pressure controlled by 5 mg of amlodipine, contraindicated to one of the drugs used in this study, patients suffering from secondary hypertension, pregnant and nursing women, recent (<6 months) MI, severe valbular heart disease or congenital heart disease, creatinine level >1.5 mg/dl for men or >1.4 mg/dl for women, significant acute illness within 14 days prior to randomization, bradycardia, SBP >180 mmHg or DBP >110 mmHg after the run-in period. A total of 80 patients fulfilling the inclusion and exclusion criteria were randomised to the amlodipine-valsartan 5/80 mg (Once daily) group and the amlodipine-atenolol 5/50 mg (Once daily) group for a period of 12 weeks. Patients were required to attend the OPD for a total of 5 visits, including 1 preinclusion visit, an inclusion visit at 0 weeks (At randomisation), and 3 follow up visits at 4 weeks, 8 weeks and 12 weeks. In the preinclusion visit, a detailed medical history was taken, a physical examination was done, blood pressure was recorded to ascertain the degree of hypertension, and in addition, they were subjected to investigations like complete blood count, urine for routine examination, serum creatinine, fasting blood sugar, fasting lipid profile, ECG and chest x-ray. All the patients were advised to follow a salt-restricted diet. On every follow-up, information regarding efficacy and tolerability was recorded. Efficacy was assessed based on the patient's blood pressure reading and tolerability based on the patient's complaints (Dizziness, fatigue, flushing, ankle oedema, and irregular heart beat) on each follow-up. All the results were expressed as mean±SD. A parametric test was done using a paired t test. Intergroup comparison of the effect of study drugs on blood pressure was done using an unpaired t test. A p-value less than 0.05 was considered significant.

RESULT

We initially screened 92 patients because the rate of dropout was lower than expected. Twelve patients (13.04%) were excluded at the end of the washout and 5 mg amlodipine run-in period, including 4 patients (33.33%) adequately controlled with 5 mg of amlodipine. After randomization, the two groups were of comparable age and blood pressure. The two groups were matched for all of the important cardiovascular risk factors.

The detailed demography showed that a larger number of patients (21.25%) in this study were found in the age group 51-60 years. The most of the patients were male (52.5%). We found that 60% of the patients in this study were from urban regions. The details of the patient's demography are given in Table-I.

Table-I: *Patient's demography, N=80*

Description	Category	Group-A Amlodipine-Valsartan, n (%)	Group-B Amlodipine-Atenolol, n (%)	Total N (%)
Age (Year)	21-30	5 (12.5)	6 (15)	11 (13.75)
	31-40	6 (15)	8 (20)	14 (17.5)
	41-50	8 (20)	7 (17.5)	15 (18.75)
	51-60	7 (17.5)	10 (25)	17 (21.25)
	61-70	9 (22.5)	6 (15)	15 (18.75)
	>70	5 (12.5)	3 (7.5)	8 (10)
Gender	Male	18 (45)	24 (60)	42 (52.5)
	Female	22 (55)	16 (40)	38 (47.5)
	Service	5 (12.5)	8 (20)	13 (16.25)
	Business	8 (20)	4 (10)	12 (15)
Occupational	Teacher	2 (5)	3 (7.5)	5 (6.25)
	Farmer	2 (5)	3 (7.5)	5 (6.25)
	Housewife	18 (45)	14 (35)	32 (40)
	Others	5 (12.5)	8 (20)	13 (16.25)
Habitat	Rural	17 (42.5)	15 (37.5)	32 (40)
	Urban	23 (57.5)	25 (62.5)	48 (60)

The prevalence of current smoking among patients was 42.5%. Only a small percentage of individuals (11.25%) had diabetes. A family history of hypertension was present in 28.75% of hypertensive individuals. We found that 47.5% of patients were taking more salt. Previous use of antihypertensive drugs was found in 67.5% of patients. The details of risk factors and clinical characteristics associated with patients are given in Table-2.

Table-II: *Risk factors and clinical characteristics associated with patients, N=80*

Description	Group-A Amlodipine-Valsartan, n (%)	Group-B Amlodipine-Atenolol, n (%)	Total N (%)
Smoking current/past or never	18 (45)/22 (55)	16 (40)/24 (60)	34 (42.5)/46 (57.5)
Habit of taking alcohol, yes/no	1 (2.5)/39 (97.5)	3 (7.5)/37 (92.5)	4 (5)/76 (95)
Family history of hypertension, yes/no	9 (22.5)/31 (77.5)	14 (35)/26 (65)	23 (28.75)/57 (71.25)
Diabetes mellitus, yes/no	3 (7.5)/37 (92.5)	6 (15)/34 (85)	9 (11.25)/71 (88.75)
Dyslipidemia, yes/no	14 (35)/26 (65)	17 (42.5)/23 (57.5)	31 (38.75)/49 (61.25)
Daily salt intake, >6gm/<6gm	13 (32.5)/27 (67.5)	25 (62.5)/15 (37.5)	38 (47.5)/42 (52.5)
Previous cardiovascular or renal disease, yes/no	2 (5)/38 (95)	5 (12.5)/35 (87.5)	7 (8.75)/73 (91.25)
Previous use of anti hypertensive drug, yes/no	26 (65)/14 (35)	28 (70)/12 (30)	54 (67.5)/26 (32.5)
ACEi or ARB	14 (54)	12 (42.8)	26 (48.1)
CCB	7 (27)	5 (17.8)	12 (22.2)
b blocker	2 (7.6)	3 (10.7)	5 (9.2)
Diuretics	2 (7.6)	7 (25)	9 (16.6)
Others	1 (3.8)	1 (3.5)	2 (3.7)

Table-III: *Change in average systolic blood pressure (SBP) values in two groups, N=80*

Group	Baseline SBP mmHg (Mean±SD)	12 Weeks SBP mmHg (Mean±SD)	Reduction in SBP mmHg (Mean±SD)	% Decrease in SBP	p-value
Group A Amlodipine-Valsartan	155.37±2.49	133.55±2.32	21.82±0.17	14.04	<0.001
Group B Amlodipine-Atenolol	154.55±2.73	140.40±2.70	14.15±0.03	9.15	<0.001

The change in systolic blood pressure in group A was from 155.37±2.49 to 133.55±2.32 mmHg and in group B from 154.55±2.73 to 140.40±2.70 mmHg. A 14.04% reduction in SBP was observed with group A and 9.15% with group B. Changes in SBP in both groups were statistically significant with a p value of <0.001 (Table-III).

The change in diastolic blood pressure in group A was from 96.92±3.20 to 80.10±1.42 mmHg and in group-B from 95.02±1.79 to 88.20±1.32 mmHg. A 17.35% reduction in DBP was observed with group A and 7.17% with group B. Changes in DBP in both groups were statistically significant with a p value of <0.001 (Table-IV).

Table-IV: *Change in average diastolic blood pressure (DBP) values in two groups, N=80*

Group	Baseline DBP mmHg (Mean±SD)	12 Weeks DBP mmHg (Mean±SD)	Reduction in DBP mmHg (Mean±SD)	% Decrease in DBP	p-value
Group A Amlodipine-Valsartan	96.92±3.20	80.10±1.42	16.82± 1.78	17.35	<0.001
Group B Amlodipine-Atenolol	95.02±1.79	88.20±1.32	6.82±0.47	7.17	<0.001

Table-V: *Change in average pulse rate values in two groups, N=80*

Group	Baseline pulse rate, bpm (Mean±SD)	12 Weeks pulse rate, bpm (Mean±SD)	Reduction in pulse rate, bpm (Mean ±SD)	% Decrease in pulse rate	p-value
Group A Amlodipine-Valsartan	73.1±10.0	70.3±11.0	2.8±11.6	3.83	>0.05
Group B Amlodipine-Atenolol	74.8±12.3	63.1±7.6	10.3±11.7	13.7	<0.05

The change in pulse rate in group A was from 73.1±10.0 to 70.3±11.0 beats per minute (bpm) which was not statistically significant. In the case of group B reduction in pulse rate was from 74.8±12.3 to 63.1±7.6 bpm, which was statistically significant. A 13.7% reduction in pulse rate was observed with group B and 3.83% with group A. Changes in pulse rate in both groups were statistically significant with a p value of <0.05 (Table-V).

DISCUSSION

The primary objective of this study was to compare the efficacy of amlodipine-valsartan to amlodipine-atenolol combination therapy in the treatment of essential hypertension. In this study, we observed that the majority of patients were in the age group of 51-60 years. It clearly shows that the prevalence of hypertension increases with age. A study conducted by Alam et al.[16] showed that a higher number of patients were in age group of 31-40 years. The present study conflicts with the observations of the above study. In the present study, a higher predominance of males (52.5%) was observed compared to females (47.5%). Our result supported by a study conducted by Kumari et al[17].

We observed that out of 80 patients, 34 (42.5%) had a habit of smoking and 5% had a habit of alcohol consumption. This was not supported by the study conducted by Preethi et al.[18] which showed that the majority of the study population had both habits of smoking and alcohol consumption (43.3%). A family history of hypertension was present in 28.75% of hypertensive individuals. This was supported by a study conducted by Alam et al[16]. New European and American guidelines recommend a target blood pressure of less than 130/80 mmHg. The ultimate goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. It was shown by the Hypertension Optimal Treatment Study (HOT study) that by reducing diastolic blood pressure to 81 mmHg instead of 84 mmHg, the number of major cardiovascular events is reduced by 51%. However, only 25% of patients with hypertension reach the target of 130/80 mmHg in routine clinical practice[19].

Clinical trial data have proved that maintaining goal blood pressure with several classes of antihypertensive agents such as ACEi, ARBs, b-blockers, calcium channel blockers and thiazide-type diuretics reduces the complications of hypertension. Most patients with hypertension require two or more antihypertensive medication to achieve their goal blood pressure. Amlodipine-valsartan reduced systolic and diastolic blood pressure from the initial mean blood pressure 155.37±2.49 mmHg/96.92±3.20 mmHg to 133.55±2.32 mmHg/80.10±1.42 mmHg after 12 weeks. Similarly, amlodipine-atenolol decreased systolic and diastolic blood pressure from the initial mean blood pressure 154.55±2.73 mmHg/95.02±1.79 mmHg to 140.40±2.70 mmHg/88.20±1.32 mmHg after 12 weeks. A 14.04% reduction in SBP was observed with the amlodipine-valsartan combination and a 9.15% reduction with the amlodipine-atenolol combination. Whereas, a 17.35% reduction in DBP was observed with the amlodipine-valsartan combination and a 7.17% reduction with the amlodipine-atenolol combination. The amlodipine-valsartan combination showed significant reductions in both systolic and diastolic blood pressure ($p<0.001$).

A significant reduction in SBP and DBP was also observed in the amlodipine-atenolol combination ($p< 0.001$). The reduction in systolic and diastolic blood pressure were greater in the amlodipine-valsartan combination group (Group-A) than in the amlodipine-atenolol combination group (Group-B) and was statistically significant ($p<0.001$). These findings are in agreement with published reports in which the amlodipine-valsartan combination has been found to be more efficacious than the amlodipine-atenolol combination in the management of hypertension[20]. Amlodipine-valsartan decreased the pulse rate from 73.1±10.0 to 70.3±11.0 beats per minute (bpm) which was not statistically significant ($p>0.05$). Similarly, amlodipine-atenolol decreased the pulse rate from 74.8±12.3 to 63.1±7.6 bpm after 12 weeks, which was statistically significant ($p<0.05$). The reduction in pulse rate was found to be greater in amlodipine-atenolol (13.7%) than in amlodipine-valsartan (3.83%) and the reduction was statistically significant ($p<0.05$). In their study, Pieree et al. discovered similar outcomes[20]. They conducted an exploratory study in France where they analysed 393 patients with essential hypertension and found that pulse rate decreased significantly more with amlodipine-atenolol (Difference: 11 bpm [95% CI: 14 to 8 bpm]; $p<0.001$). Although the assessment of the risk factor was not an objective of the study, it was totally based on the patient interview. In this study, the impact of the non-pharmacological treatment was not considered. However the methodology of the study was followed properly. No patients reported any adverse drug reactions (ADR's) to any prescribed antihypertensive drugs in our study. It indicates that all of the patients tolerated the prescribed drugs and doses. Lifestyle modifications decrease blood pressure, increase antihypertensive drug efficacy, and decrease cardiovascular risk. Along with drug therapy and lifestyle modifications such as weight reduction, reduced salt intake, regular exercise, avoiding smoking

and alcohol and avoiding stress we can effectively control blood pressure. At the end of our study, we educated patients regarding disease and lifestyle modifications to be followed for control of high blood pressure and prevention of further complications.

CONCLUSION

Our analysis revealed the different efficacy of drugs on blood pressure reduction when using the two kinds of drug combinations. The available conclusion from our analysis suggests that the amlodipine-valsartan combination possesses higher blood pressure reduction efficacy than the amlodipine-atenolol combination. However, in terms of pulse rate reduction, amlodipine-atenolol combination is more effective. The availability of a single-pill fixed-combination of amlodipine-valsartan and amlodipine-atenolol for the treatment of essential mild to moderate hypertension represents an important step forward. Further studies with a large number of patients covering different regions of Bangladesh are needed to extrapolate these findings. We also recommended that the design of such a study include effects from non-pharmacological treatment, and patients should be followed for a longer periods of time to obtain the long-term effects of drugs in terms of safety and efficacy.

LIMITATIONS

The main limitation of this study is the small sample size. Patients were followed only for 12 weeks, and the impact of non-pharmacological treatment in this study was not taken into account.

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