

EFFICACY OF VALSARTAN PLUS AMLODIPINE VERSUS VALSARTAN PLUS HYDROCHLOROTHIAZIDE FOR CONTROL OF MODERATE TO SEVERE HYPERTENSION: A RANDOMIZED CONTROLLED TRIAL

Muhammad Habeel Dar¹, Shiekh Fahad Falah², Imran khan³,
Adnan khan⁴, Umair Ali⁵

^{1,2,5}Department of Cardiology, Lady Reading Hospital Peshawar-Pakistan
³ Department of Cardiology, Hayatabad Medical Complex, Peshawar-Pakistan.
⁴ Rehman Medical Institute, Peshawar-Pakistan.

Address for Correspondence:

Muhammad Habeel Dar

Department of Cardiology, Lady Reading Hospital Peshawar-Pakistan

E-Mail: habeeldar1978@gmail.com

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Contribution

MHD, SFF conceived the idea, designed and conducted the study and analyzed the data. IK, AK helped in acquisition of data and did statistical analysis. UA did critical review. All authors contributed significantly to the submitted manuscript.

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ABSTRACT

Objective: To compare of the efficacy of valsartan plus amlodipine versus valsartan plus hydrochlorothiazide for control of moderate to severe hypertension

Methodology: This randomized controlled trial was conducted at Department of Cardiology, Lady Reading Hospital Peshawar from 1st January, 2015 to 30th June, 2015. All patients with stage 2 hypertension of either gender were randomly assigned into two groups. Patients in group A were subjected to combination of valsartan 160 mg plus amlodipine 10 mg and patients in group B were subjected to the combination of valsartan 160 mg plus hydrochlorothiazide 25 mg. Patients were selected by non probability purposive technique. All patients were followed for 4 weeks.

Results: A total of 88 patients were included in this study. Mean age in both groups was 65 ± 1.26 years. In group A, 27 (62%) patients were males, where as in group B, 26 (60%) patients were males. Valsartan + Amlodipine was effective in 32 (72%) cases and was not effective in 12 (28%) cases while Valsartan + Hydrochlorothiazide was effective in 35 (80%) cases and was not effective in 9 (20%) cases ($p=0.2$).

Conclusion: Both combinations had similar anti-hypertensive effects, however Valsartan + Hydrochlorothiazide combination had a better therapeutic profile as it showed fewer side effects and less treatment dropout than Valsartan + Amlodipine combination.

Key Words: Efficacy, Valsartan plus amlodipine, Valsartan plus hydrochlorothiazide, Hypertension

INTRODUCTION

Hypertension is one of the leading causes of death around the globe and has emerged as an increasingly important medical and public health issue. It affects approximately 25% of the adult population worldwide, and its prevalence is predicted to increase by 60% by year 2025. It is a major treatable risk factor for coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure and peripheral arterial disease (PAD); and accounts for 6% of deaths worldwide.³ The prevalence of hypertension increases with age. Approximately more than half of people aged 60 to 69 years and three-fourths of those aged 70 years and older have hypertension. The increase in incidence and prevalence of hypertension with increasing age is primarily due to age-related rise in systolic blood pressure (SBP). SBP rises uninterruptedly with age and appears as a strong independent risk-factor of cardiovascular, cerebral and renal complications.

Sufficient evidence now has accumulated suggestive of SBP being the most important determinant of risk in hypertensive patients, especially in elderly patients. Increased peripheral resistance that is caused by arterial vasoconstriction, traditionally has been viewed as the key determinant of diastolic blood pressure (DBP). In fact, the early releases of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defined hypertension on the basis of elevated DBP values only. This resulted in the long-standing conviction that the cardiovascular risks associated with hypertension derive principally from the diastolic component of blood pressure (BP).

SBP has the tendency to rise continuously throughout life, while DBP rises up to approximately 50 years of age, then levels off and tends to decrease after the age of 60. Franklin et al prospectively collected database of the Framingham heart study carried out in 9657 adults who were free from cardiovascular disease (CVD) and without antihypertensive therapy, the authors confirmed that SBP is a stronger risk factor for CVD than DBP. Moreover, the authors demonstrated that the combined evaluation of SBP and DBP improves cardiovascular risk prediction over the two individual components.

The burden of cardiovascular morbidity and mortality can be reduced by prevention and treatment of isolated systolic hypertension (ISH). There is now compelling evidence from cross-sectional, longitudinal and randomized controlled trials that shows that ISH confers a substantial cardiovascular risk. ISH leads to a two-fold increase in risk of cardiovascular accidents as well as acute myocardial infarction (MI). According to the Seventh Report of the Joint National Committee (JNC-7) on prevention, detection, evaluation and treatment of high blood pressure, SBP of

greater than 140 mmHg is a more important CVD risk factor than DBP in those older than age 50 years. Clinical trials and observational studies suggest that poor SBP control is largely responsible for the unacceptably low rates of overall BP control. Interestingly SBP control rates were considerably less (60 to 70%) while DBP control rates exceeded 90% in the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

The ongoing studies in Pakistan will elucidate the effect of newly available AT1 receptor antagonist like telmisartan on cardiovascular mortality along with reduction in target organ damage in essential hypertension as compared to angiotensin converting enzyme inhibitors (ACEIs).

The objective of this study was to compare the efficacy of valsartan plus amlodipine versus valsartan plus hydrochlorothiazide for control of moderate to severe hypertension.

METHODOLOGY

This randomized control trial study was conducted at the Department of Cardiology Lady Readings Hospital Peshawar from 1st January to 30th June, 2014. Patients were selected by non probability purposive technique. All patients with stage 2 hypertension of both gender, with ages between 35-90 years were selected. Patients with known secondary hypertension, allergic to valsartan amlodipine or hydrochlorothiazide, already on multiple medications and patients with co morbidities like diabetes, ischemic heart disease were excluded from the study.

The study was conducted after approval from hospital's ethical and research committee. All patients with hypertension and having BP greater than 160/100 mmHg were included in the study.

The patients with clinical suspicion of secondary hypertension were screened for chronic kidney disease by measuring GFR, for coarctation of aorta by measuring BP in legs, for endocrine disease by measuring serum cortisol and serum aldosterone levels, and for pheochromocytoma by serum free metanephrine levels. ECG and echocardiography were done for ischemic heart diseases, valvular diseases and congestive heart failure.

All patients were subjected to detailed history and clinical examinations. All patients were randomly assigned in two groups by lottery method. Patients in groups A were subjected to combination of valsartan 160 mg and amlodipine 10 mg and patients in group B were subjected to the combination of valsartan 160 mg and hydrochlorothiazide 25 mg. Both drugs were given in single pill of the same pharmaceutical company and were given free from ward fund. Labels were removed from the drugs so that patients

and investigators were unaware of the type of medicine given. Tablets were counted and undertaking was taken from the attendant so that it is ensured that drug is given in morning regularly.

All patients were followed for 4 weeks and blood pressure readings were obtained at interval of 2 and 4 weeks. Reading was taken by method defined in the BHS guidelines. Patients were refrained from smoking or ingesting caffeine about 30 minutes before measurement was taken. Mean of 3 readings, separated by 2 min was recorded in both arms by Yamasu mercury sphygmomanometer. All information including baseline characteristics was recorded in pre designed proforma. Strict exclusion criteria was followed to control confounders and bias in the study results.

Data was entered and analyzed by statistical package for social science (SPSS) version 19. Mean + SD was calculated for numerical variables like age, baseline blood pressure readings and follow up Blood Pressure Readings. Frequencies and percentages were calculated for categorical variables like gender and efficacy. Chi square test was used for categorical variables and student-T test for numerical variables. P value of 0.05 was taken as significant. All results were presented in the form of tables and graphs.

RESULTS

Total of 88 patients were observed to compare of the efficacy of valsartan plus amlodipine versus valsartan plus hydrochlorothiazide for control of moderate to severe hypertension.

In group A mean age was 65 ± 1.26 years. About 5(11%) patients were in range of 35-45 years, 10(23%) patients in range of 46-55 years, 20(45%) patients in range of 56-65 years and 9(21%) patients in range of 66-75 years. Where as in group B mean age was 65 ± 1.26 years. About 5(11%) patients were in range of 35-45 years, 10(23%) patients in range of 46-55 years, 20(45%) patients in range of 56-65 years and 9(21%) patients were in range of 66-75 years. Group A consisted of 27(62%) male patients while group B had 26(60%) male patients as shown in Figure 1.

About 15(35%) patients were diabetics in group A while 17(38%) patients were diabetic in group B as shown in Figure 2.

Efficacy analysis of both groups showed that Valsartan + Amlodipine was effective in 32(72%) cases while Valsartan + Hydrochlorothiazide was effective in 35(80%) cases as shown in Table 3.

Figure: 1 Gender Distribution of Two Groups in Study Population (n=88)

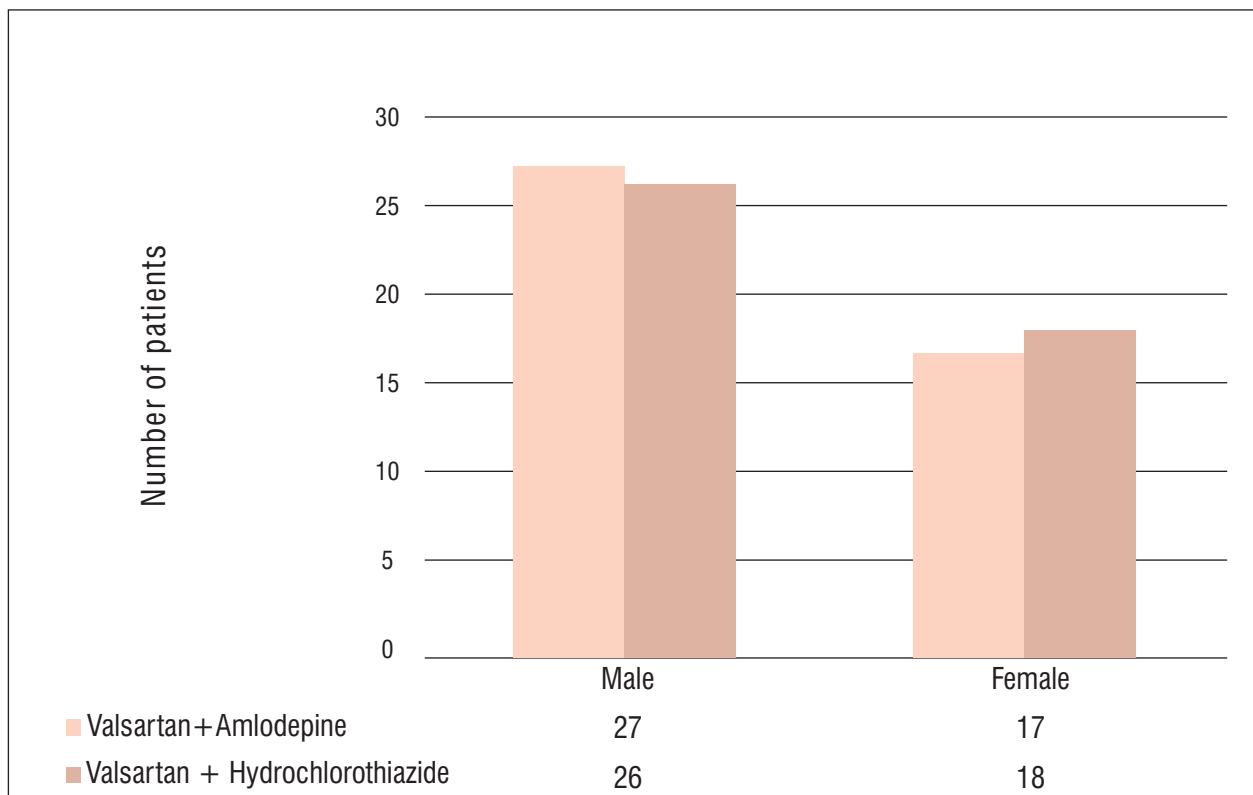
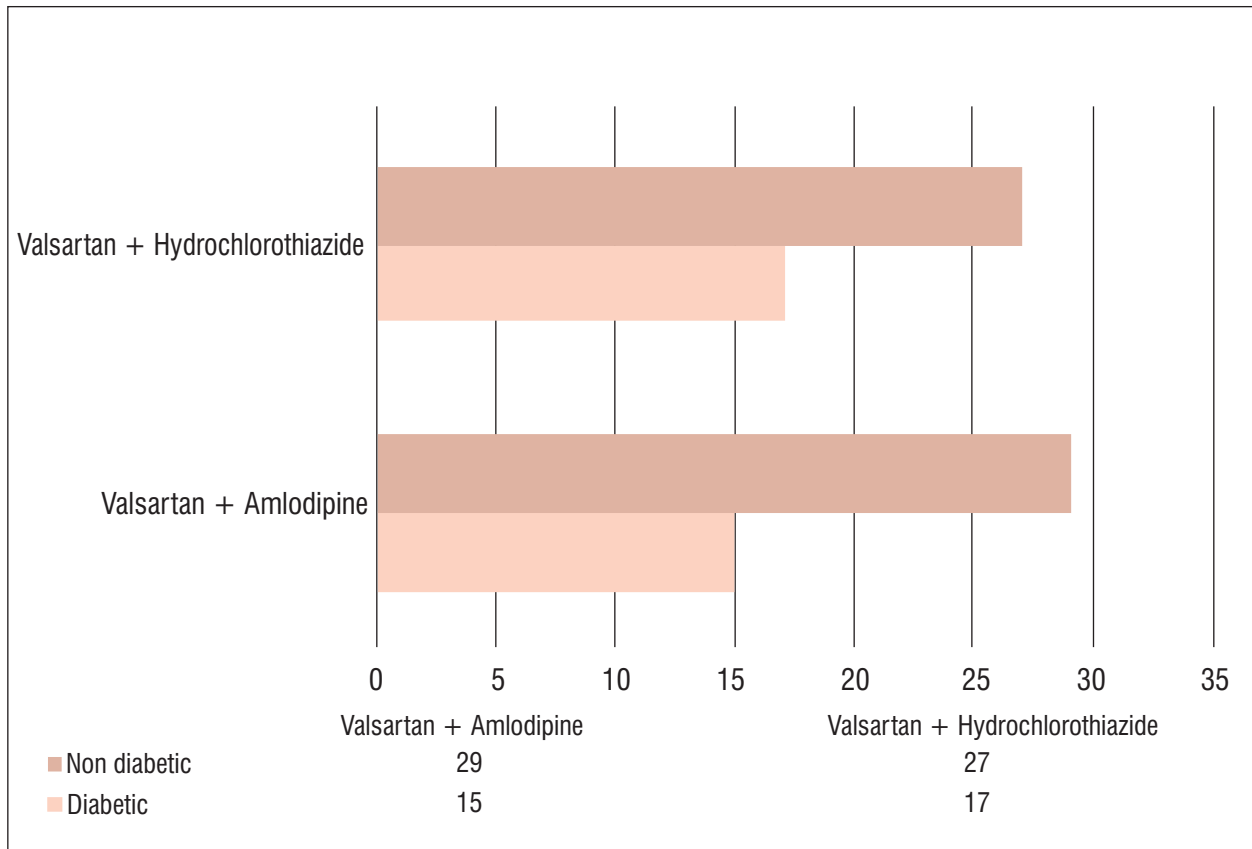


Figure 2: Distribution Of Diabetes Mellitus In Study Population (n=88)

Baseline blood pressure in two groups was analyzed. About 23(53%) patients had systolic BP of 160-170 mm of Hg, 14(32%) had systolic BP of 170-180 mm of Hg, and 7 (15%) patients had systolic BP of 180-190 mm of Hg in group A. While 26(58%) patients had diastolic BP of 100-105 mm of Hg, 13(30%) patients had diastolic BP of 106-110 mm of Hg, and 5 (12%) patients had diastolic BP of 110-120 mm of Hg. Where as in group B 22(50%) patients had systolic BP of 160-170 mm of Hg, 16(37%) patients had systolic BP of 170-180 mm of Hg, and 6 (13%) patients had systolic BP of 180-190 mm of Hg. While 24(55%) patients had diastolic BP of 100-105 mm of Hg, 15(33%) patients had diastolic BP of 106-110 mm of Hg, 5(12%) patients had diastolic BP of 110-120 mm of Hg as shown in table 1.

Blood pressure on 2nd week follow up of two groups was analyzed. In group A 27(61%) patients had systolic BP of 140-150 mm of Hg, 10(23%) with systolic BP 151-160 mm of Hg, and 7 (16%) with systolic BP of 161-180 mm of Hg. More over 24(55%) patients had diastolic BP of 90-100 mm of Hg, 16(35%) had diastolic BP of 101-105 mm of Hg, and 4 (10%) had diastolic BP of 106-110 mm of Hg. Where as in group B 29(65%) patients had systolic BP range 140-150

mm of Hg, 10(22%) had systolic BP of 151-160 mm of Hg, and 5 (13%) patients had systolic BP of 161-180 mm of Hg. More over 26(60%) patients had diastolic BP of 90-100 mm of Hg, 15(33%) patients had diastolic BP of 101-105 mm of Hg, and 3 (7%) patients had diastolic BP of 106-110 mm of Hg (Table 1).

Follow-up blood pressure at 4th week of two groups was analyzed. In group A, 32(72%) patients had systolic BP of <140 mm of Hg, 9(21%) had systolic BP of 141-150 mm of Hg, 3(7%) had systolic BP of 151-160 mm of Hg. While 31(70%) patients had diastolic BP range < 85 mm of Hg, 10(23%) patients had diastolic BP of 86-90 mm of Hg, and 3 (7%) patients had diastolic BP of 90-100 mm of Hg. Where as in group B 35(80%) patients had systolic BP of <140 mm of Hg, 7(16%) patients had systolic BP of 141-150 mm of Hg, 2(4%) patients had systolic BP of 151-160 mm of Hg. More over 35(79%) patients had diastolic BP of < 85 mm of Hg, 8(19%) patients had diastolic BP of 86-90 mm of Hg, and 1 (2%) patient had diastolic BP of 90-100 mm of Hg. (Table 2).

Table 1: Blood Pressure at Baseline And 2nd Week Of Follow Up In Study Population (n=88)

| Blood Pressure | | Base line BP n(%) | | 2nd week follow-up | |
|-------------------------|---------|---------------------------------------------|-------------------------------------------------------|---------------------------------------------|------------------------------------------------------|
| Mean \pm SD | | Valsartan + Amlodipine 175 \pm 3.66 | V alsartan + Hydrochlorothiazide 180 \pm 4.11 | Valsartan + Amlodipine 155 \pm 4.72 | Valsartan + Hydrochlorothiazide 150 \pm 3.82 |
| Systolic (mm of Hg) | 160-170 | 23(53%) | 22(50%) | 27(61%) | 29(65%) |
| | 170-180 | 14(32%) | 16(37%) | 10(23%) | 10(22%) |
| | 180-190 | 7(15%) | 6(13%) | 7(16%) | 5(13%) |
| Total | | 44 | 44 | 44 | 44 |
| Diastolic (mm of Hg) | 100-105 | 26(58%) | 24(55%) | 24(55%) | 26(60%) |
| | 106-110 | 13(30%) | 15(33%) | 16(35%) | 15(33%) |
| | 110-120 | 5(12%) | 5(12%) | 4(10%) | 3(7%) |
| Total | | 44 | 44 | 44 | 44 |
| Mean \pm SD | | 110 \pm 5.73 | 109 \pm 2.53 | 101 \pm 5.79 | 100 \pm 4.76 |

Table 2: Blood Pressure At 4th Week Follow Up In Study Population (n=88)

| 4 th Week follow -up | | Valsartan + amlodipine n(%) | Valsartan + Hydrochlorothiazide n(%) |
|---------------------------------|----------|--------------------------------|-----------------------------------------|
| Systolic (mm of Hg) | < 140 | 32 (72 %) | 35 (80%) |
| | 141 -150 | 9(21 %) | 7(16 %) |
| | 151 -160 | 3(7%) | 2(4%) |
| Total | | 44 | 44 |
| Mean \pm SD | | 145 \pm 2.35 | 138 \pm 1.94 |
| Diastolic (mm of Hg) | < 85 | 31 (70 %) | 35 (79 %) |
| | 86 -90 | 10 (23 %) | 8 (19 %) |
| | 90 -100 | 3(7%) | 1(2%) |
| Total | | 44 | 44 |
| Mean \pm SD | | 90 \pm 2.72 | 82 \pm 1.83 |

Table 3: Efficacy Of Drugs In Study Population (n=88)

| Efficacy | Valsartan + Amlodipine | Valsartan+ Hydrochlorothiazide | TOTAL | p-value |
|---------------|------------------------|--------------------------------|-------|---------|
| Effective | 32 (72%) | 35 (80%) | 67 | |
| Not Effective | 12 (28%) | 9 (20%) | 21 | 0.229 |
| Total | 44 | 44 | 88 | |

DISCUSSION

In this study, we assessed the antihypertensive effects of valsartan, one of the most extensively studied ARBs, when combined with the diuretic hydrochlorothiazide (HCTZ) or the CCB amlodipine as first-line treatment of hypertension and its associated comorbidities. Previous studies involving amlodipine/valsartan have studied its effect on BP. No previous outcome studies are available on the first-line use of valsartan/HCTZ. Previously HCTZ was studied as a possible add-on therapy to valsartan, showed the benefits of this treatment on cardiovascular morbidity and mortality.²² Valsartan therapy has also shown benefits in patients of chronic heart failure and post-myocardial infarction. Studies have shown use of valsartan/HCTZ and amlodipine/valsartan, in the treatment of hypertension and the rationale for the use of single-pill combinations.

Two 8-weeks, placebo-controlled studies compared the antihypertensive efficacy of valsartan/ HCTZ versus monotherapy. Combination therapy was beneficial as compared to the corresponding monotherapies. The second placebo-controlled study investigated the anti-hypertensive efficacy of valsartan and HCTZ alone and in combination at doses up to 320/25 mg in 1346 patients with diastolic BP of 95 mmHg and 110 mmHg. For all efficacy parameters, combination therapy provided significantly greater antihypertensive efficacy relative to placebo and the corresponding monotherapies ($p = 0.05$).

The combination of valsartan / HCTZ is well tolerated and adverse events are generally mild and transient. A meta-analysis of the results of 9 randomized, double-blinded, placebo-controlled, hypertension studies (n=4278) of once daily valsartan 80, 160, or 320 mg or valsartan / HCTZ 80/12.5, 160/12.5 mg, 160/25 mg, 320/12.5 mg, or 320/25 mg given for 4 to 8 weeks showed lesser side effects."

The addition of a RAAS blocker may help to reduce this effect because it causes dilation of both arterial and venous capillary beds, thus bringing trans-capillary pressure back

to normal. During this time, peripheral edema was reported in 31.1% of patients on high-dose amlodipine compared with only 6.6% of patients on combination therapy.

In our study shows that Valsartan + Amlodipine was effective in 72% cases while Valsartan + Hydrochlorothiazide was effective in 80% cases. The comparison between the two associations showed no statistical difference in lowering the systolic BP and diastolic BP. The combination of Valsartan + Hydrochlorothiazide had more complains of dizziness when compared to Valsartan + Amlodipine (OR: 2.08–95% CI -1.54 to 2.80). On the other hand the combination with amlodipine generated more edema (OR: 16.19–95% CI 7.61–34.4). There was no difference between the therapies regarding headache (OR: 1.00, 95% CI 0.78–1.30). When analyzing the variable "any side effects", Valsartan + Amlodipine had an OR of 2.63 (95% CI 2.32–2.98) when compared to Valsartan + Hydrochlorothiazide, showing that the combined therapy with amlodipine had more side effects. The combination of Valsartan + Amlodipine had a greater chance of discontinuity in comparison with Valsartan + Hydrochlorothiazide, since the odd of treatment discontinuity was 1.20 (95% CI 1.02–1.41). There was no statistical difference in the data regarding the lowering of blood pressure between Valsartan + Hydrochlorothiazide and Valsartan + Amlodipine.

CONCLUSION

Although the two combinations have similar antihypertensive effects, Valsartan + Hydrochlorothiazide has a better therapeutic profile as it showed fewer side effects and less treatment dropout than Valsartan + Amlodipine association.

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