

# Efficacy and Tolerability of Valsartan and Hydrochlorothiazide versus Valsartan and Amlodipine in Stage 2 Hypertension

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## ABSTRACT

**Background:** Hypertension is a growing medical and public health issue. United States and European treatment guidelines have been issued to attain smooth control of hypertension in various categories of patients. It is the need of the time to unveil the safe combination therapies in various populations.

**Objective:** (i) To determine the efficacy of valsartan and hydrochlorothiazide versus valsartan and amlodipine (ii) To determine the safety and tolerability of both combinations.

**Materials & Methods:** This experimental study was conducted at Shalamar Hospital Lahore. 126 patients of stage 2 hypertension were recruited from the medical outdoor of Shalamar Hospital Lahore after getting informed consent. In group A, 63 patients were given valsartan and hydrochlorothiazide. In group B, 63 patients were given valsartan and amlodipine. Blood pressure (BP) of both study groups was recorded on day zero, 2<sup>nd</sup>, 4<sup>th</sup>, and 8<sup>th</sup> weeks and the readings were entered on a Performa. The efficacy of drug combinations was accessed in both groups by recording the change in mean systolic blood pressure (MSBP) and mean diastolic blood pressure (MDBP). Safety and tolerability of the drug combinations was assessed in terms of side effects and laboratory findings.

**Results:** In group A, there was 39±7mmzHg and 18±1mmHg decrease in MSBP and MDBP respectively from base line BP. In group B, there was 26.7±4mmHg and 14±2 mmHg decrease in MSBP and MDBP respectively from base line BP. Both combinations were safe and no significant difference in the efficacy of both combinations was observed after 8-week of treatment.

**Conclusion:** Both combinations are effective for control of BP, but valsartan and hydrochlorothiazide combination (group A) appears to have better tolerability and greater effect in decreasing BP as compared to combination of valsartan and amlodipine (group B),although this difference is not statistically significant.

**Key Words:** Amlodipine, antihypertensive drugs, efficacy, valsartan, hydrochlorothiazide

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## INTRODUCTION

Hypertension is a growing medical and public health issue around the globe and the main cause of disability and mortality. Improving hypertension management remains one of the most difficult tasks globally.

As a result, how to effectively control hypertension based on unique patient characteristics, with non-pharmacological and pharmacological approaches has become problematic and has to be addressed immediately.<sup>1</sup>

United States and European treatment guidelines have been issued to attain smooth control of

hypertension in different patients. These guidelines, on the other hand, suggest that they may be used to help healthcare professionals in their routine practice. The final choice for an individual patient must be made by skilled health professionals in consultation with the caregiver and patient, if appropriate.<sup>2</sup>

When mean diastolic blood pressure (MDBP) is  $\geq 90$  mmHg and mean systolic blood pressure (MSBP) is  $\geq 140$  mmHg, it is classified as stage 2 hypertension. The 7<sup>th</sup> report of the Joint National Committee on prevention, detection, and treatment of hypertension recommends that individuals with stage 2 hypertension need to be treated with a combination of two drugs from different classes.<sup>3</sup>

According to the literature, fixed-dose combinations are more effective, well-tolerated, safe, and cost-effective than monotherapy. Yet further studies are needed to determine the best combination therapy for diverse groups based on race, gender, age, and comorbidities.<sup>4</sup>

Blood pressure should be monitored regularly. Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs) should be used in conjunction with calcium channel blockers (CCBs) or thiazide diuretics, according to European hypertension guidelines.<sup>5</sup> According to these guidelines replacing hydrochlorothiazide with amlodipine had many metabolic and cardiovascular benefits.<sup>6</sup> In another trial, losartan and amlodipine were found to be more effective at regulating blood pressure (BP) than losartan and hydrochlorothiazide.<sup>7</sup>

In a clinical trial, Kondo et al. found that combining telmisartan and amlodipine or telmisartan and hydrochlorothiazide reduced BP effectively in patients with uncontrolled hypertension previously receiving angiotensin II receptor blockers only.<sup>8</sup> In a study from Africa reported that either perindopril or hydrochlorothiazide with amlodipine were more effective than perindopril plus hydrochlorothiazide in decreasing blood pressure

after 6 months of treatments.<sup>9</sup> Hypertension is a very common disease, so general physicians need to familiarize themselves with best practices in blood pressure control to become better advocates of evidence-based medicine.

Hence, the study was designed to determine the efficacy of valsartan and hydrochlorothiazide versus valsartan and amlodipine along with the safety and tolerability of both combinations.

## MATERIALS AND METHODS

This experimental study was carried out at the Medicine Department of Shalamar Hospital Lahore. A purposive sampling technique was used. Ethical approval was granted by the Institutional Review Board of Shalamar Medical & Dental College, Lahore.

126 patients with stage 2 hypertension having  $BP \geq 140/90$  mm Hg were recruited from the medical outdoors of Shalamar Hospital after getting informed consent. The patients were randomly allocated to group A and group B. Both groups included patients from both genders aged 35-65 years, having stage 2 hypertension with  $MDBP \geq 90$  mmHg and  $MSBP \geq 140$  mmHg in the sitting position. The patients who had secondary hypertension, hypertensive crises, advanced heart failure, renal or hepatic disease, past history of myocardial infarction, stroke, transient ischemic attack, or angioplasty in the last six months and taking more than 2 antihypertensive drugs were excluded from the study.

Baseline blood pressure was recorded at day "0" and 5 ml venous blood was drawn for laboratory investigations of biochemical parameters before prescribing the combination therapy. In group A, 63 patients were prescribed oral valsartan and hydrochlorothiazide 160/12.5 mg once daily. In group B, 63 patients were prescribed oral valsartan and amlodipine 160/5 mg once daily. Patients were advised to come for follow-up of BP, laboratory investigations, and side effects at 2<sup>nd</sup>, 4<sup>th</sup>, and 8<sup>th</sup> week.

The British Hypertension Society (BHS) guidelines were followed for taking blood pressure readings. The patients were asked to avoid smoking or consuming coffee for about 30 minutes before recording of blood pressure. A mercury sphygmomanometer was used to record three readings of blood pressure and then the average of the three readings was calculated.<sup>11</sup>

Blood samples were collected and reported by the Shalamar Hospital laboratory.

The efficacy variables in both groups, to assess the equivalence of therapeutic efficacy of the two regimens are:

1. the change in mean sitting systolic blood pressure (MSBP)
2. the change in mean sitting diastolic blood pressure (MDBP)
3. Control rate is defined as the proportion of patients achieving mean diastolic blood pressure  $\leq 90$  mmHg.<sup>12,13</sup>

Safety was determined by exploring the side effects (either reported by patients or asked by the physicians), clinical examination, and laboratory reports on 2<sup>nd</sup>, 4<sup>th</sup> and 8<sup>th</sup> week.

### Statistical Analysis

The data was analyzed by SPSS version 22.0. Comparison between the two groups was done by applying a t-test and Chi-square ( $\chi^2$ ) test accordingly p-value  $\leq 0.05$  was taken as significant.

## RESULTS

The mean age of patients in groups A and B was  $52 \pm 10$  and  $53 \pm 09$  years respectively. In group A 68% of patients were female and 32% were male while in group B 83% of patients were female and 17 % were male. The mean weight of patients in group A was  $76 \pm 18$  kg and in group B was  $75 \pm 19$  kg body weight.

Efficacy analysis of both groups showed that both combinations were effective in controlling blood pressure. Baseline BP was recorded in both groups. Baseline MSBP and MDBP in group A were  $160.9 \pm 14$  and  $94.8 \pm 6$  mmHg respectively. In group B, MSBP and MDBP were  $151.7 \pm 13$  and  $91.2 \pm 7$  mmHg respectively. (Figure 1)

In both groups, there was a decrease in systolic and diastolic BP on each visit as shown in table 1 and 2 respectively. In group A taking valsartan and hydrochlorothiazide, there was a  $39 \pm 7$  and  $18 \pm 1$  decrease in MSBP and MDBP from baseline respectively. While in group B taking valsartan and amlodipine, there was a  $26.7 \pm 4$  and  $14 \pm 2$  decrease in MSBP and MDBP from baseline respectively (Table 1).

The efficacy of treatment in reducing MSBP was 100% and 97.6% (p=0.47) in group A and group B respectively) after 8 weeks of treatment and this reduction in MDBP was 100% (p=0.99) in both groups (Table 2) significant statistically.

**Table 1: Decrease in Systolic and Diastolic Blood Pressure Measured on Each Visit in Group A & Group B**

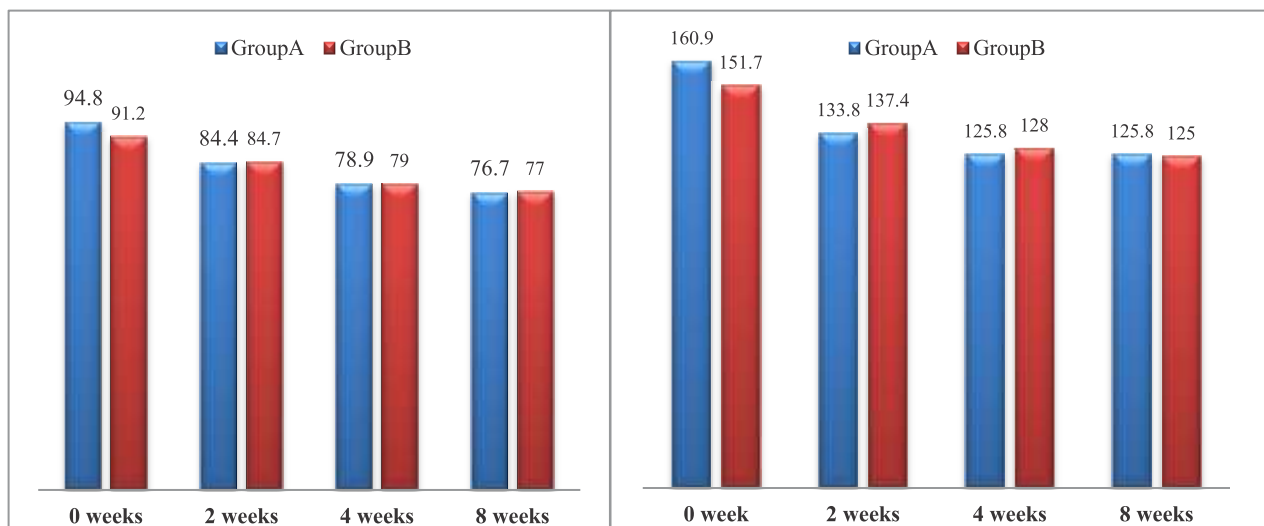
	Variables	Groups A (mean $\pm$ SD)	Groups B (mean $\pm$ SD)	P-value
<b>Baseline</b>	Systolic BP	160.9 $\pm$ 14	151.7 $\pm$ 13	0.01*
	Diastolic BP	94.8 $\pm$ 6	91.2 $\pm$ 8	0.03*
<b>2 weeks</b>	Systolic BP	133.8 $\pm$ 13	137.4 $\pm$ 16	0.27
	Diastolic BP	84.4 $\pm$ 8	84.7 $\pm$ 7	0.85
<b>4 weeks</b>	Systolic BP	125.8 $\pm$ 10	128 $\pm$ 10	0.23
	Diastolic BP	78.9 $\pm$ 8	79 $\pm$ 7	0.96
<b>8 weeks</b>	Systolic BP	121.9 $\pm$ 7	125 $\pm$ 9	0.06
	Diastolic BP	76.7 $\pm$ 5	77 $\pm$ 6	0.07
<b>Decrease in SBP on 8<sup>th</sup> week from baseline</b>		39 $\pm$ 7	26.7 $\pm$ 4	0.47
<b>Decrease DSBP in 8<sup>th</sup> week from baseline</b>		18 $\pm$ 1	14 $\pm$ 2	0.66

*t-test was applied; p<0.05 was considered statistically significant*

**Table 2: Comparison of Patients Achieving mean SBP<140mmHg and DBP≤90 mmHg**

Groups	SBP <140 mmHg		p-value	DBP ≤90 mmHg		p-value
	Yes	No		Yes	No	
A	63(100%)	0	0.47	63(100%)	0	0.99
B	61(97.6%)	2(2.4)		63(100%)	0	

Chi-square test was applied; P<0.05 was considered statistically significant



**Fig: Mean Systolic Blood pressure and Diastolic blood pressure of Group A & B**

**Table 3: Comparison of Biochemical Parameters in Group A and B to Access the Safety of Both Drug Combinations**

Level of serum	Group A			Group B		
	0 week	8 week	p-value	0 week	8 week	p-value
Sodium(mmol/l)	138.8	138.5	0.41	139.4	139.1	0.43
Potassium(mmol/l)	4.21	4.81	0.95	4.20	4.20	0.83
Chloride(mmol/l)	100.5	100.7	0.83	99.3	99.3	0.04
Creatinine(mg/dl)	0.86	0.93	0.06	1.03	0.96	0.78
cholesterol(mg/dl)	150.1	150.7	0.01	175.1	175.5	0.02
Sugar(R) (mg/dl)	151.0	153.0	0.53	145.9	145.1	0.31
Urea(mg/dl)	3.53	3.57	0.33	3.7	3.3	0.58

**Table 4: Comparison of Side Effects of Both Drug Combinations in Group A and B**

Side effects Groups	0 Week		2 <sup>nd</sup> Weeks		4 <sup>th</sup> Weeks		8 <sup>th</sup> Weeks	
	A (%)	B (%)	A (%)	B (%)	A (%)	B(%)	A (%)	B (%)
Pedal edema	0	0	5	10	5	15	0	15
Cough	0	0	8	6	6	1	0	0
Headache	0	3	18	16	11	2	1	0
myalgia	1	3	16	10	15	1	3	0
Diarrhoea	0	0	1	1	1	0	0	0
Lethargy	1	0	11	14	11	2	1	0
Rash	0	0	0	0	0	0	0	0

0 = No case reported

Safety and tolerability were assessed by the appearance of side effects and derangement of biochemical parameters as shown in table 3 & 4 respectively. In either of the combination headache, myalgia, lethargy, cough, and edema was noted in few patients in 2<sup>nd</sup> and 4<sup>th</sup> week but it disappeared on 8<sup>th</sup> week in all the patients. But the edema persisted in 15% patients taking valsartan and amlodipine till 8<sup>th</sup> week.

Myalgia was observed in very few patients taking valsartan and hydrochlorothiazide combination (3%). There was no significant derangement of biochemical parameters in both groups.

## DISCUSSION

The blood pressure-lowering effect of valsartan, when paired with hydrochlorothiazide or amlodipine, as first choice hypertension therapy was evaluated and compared in this study. According to a meta-analysis, combination therapy provides smooth blood pressure regulation, fewer side effects, and better tolerance in hypertensive patients than monotherapy.<sup>14</sup>

Both combinations are recommended by JNC, but it has been suggested that further research is required to finalize the choice of combination therapies in different populations based on race, gender, and age. So, it was observed in this study that both combinations are effective for the smooth control of blood pressure in our population. These results are in accordance with

study of Poldermas et al., which found that combinations of amlodipine and valsartan was well tolerated and more effective.<sup>15</sup> In our study efficacy of valsartan and hydrochlorothiazide was not found to be significantly higher than valsartan and amlodipine combination, which is contradictory with a study done in 2017.<sup>16</sup> The current study has shown that combination of fixed-dose valsartan and hydrochlorothiazide was safer and better tolerated.

The patients who received combination of valsartan and hydrochlorothiazide had more complains of headache, lethargy and myalgia when compared with patients taking valsartan and amlodipine in first two weeks. However, combination of amlodipine and valsartan also showed edema, headache, and myalgia in first two weeks, but these side effects decreased on 8<sup>th</sup> week except peripheral edema which persisted even after 8 weeks. This high incidence of peripheral edema with amlodipine combination was also observed in another study.<sup>17</sup>

In present study edema disappeared in the group taking valsartan and hydrochlorothiazide, which is consistent with the findings of Matthew.et.al. According to their study angiotensin receptor blockers and angiotensin-converting enzyme inhibitors cause post-capillary dilation and normalize hydrostatic pressure, making them ideal for preventing/reversing calcium channel blocker-induced edema.<sup>18</sup>

In the present study, it was found that a combination of Valsartan and Hydrochlorothiazide is better tolerated than a combination of Valsartan and amlodipine.<sup>19</sup>

It was a single-center study, which may have reduced the chances of identifying the genuine benefits of those therapies.

## CONCLUSION

Both combinations are effective for the control of BP, but the valsartan and hydrochlorothiazide combination appears to be more effective in decreasing BP and better tolerated as compared to the combination of valsartan and amlodipine.

## Recommendations:

The current study looked at 'soft' endpoints and was non-inferiority based, thus more Research is needed to see which sort of valsartan-based combination is superior in big samples from different centers of the country.

## Conflict of interest:

All authors declared no conflicts of interest.

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## Contributors:

**AK:** Study design, manuscript writing, revised and approved the article.

**SI:** Primary drafting, data analysis and result

**MRA:** entered, analyzed, and interpreted data

**SAB:** contributed to the writing of literature review

**NI & AE:** Data collection, result, discussion

All authors approved the final version and signed the agreement to be accountable for all aspects of the work.

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