

## **An observational comparative study of different doses of azilsartan and with chlorthalidone combination in moderate hypertension**

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### **ABSTRACT**

**Background:** High blood pressure (BP) is one of the significant non-communicable diseases that are of high prevalence in our country. Hypertension (HTN) is responsible cause of 57% of stroke and 24% of coronary heart disease deaths in India. Eight classes of medications are currently used in the treatment of hypertension. Azilsartan medoxomil is a newly added FDA approved drug to the ARB class of antihypertensive agents. azilsartan and chlorthalidone combination is also got the FDA approval. There is limited study in between these two groups regarding efficacy especially in rural Bengal.

**Methods:** A prospective observational study was done in medicine OPD of Bankura Sammilani Medical College for twelve weeks with two groups that are azilsartan (80mg) and fixed dose combination of azilsartan (40mg) plus chlorthalidone (12.5mg) in the age group of 18 to 55years of moderate hypertensive patients. Change of heart rate was assessed as safety parameter.

**Results:** It was found that both the group of drugs are very much effective in lowering blood pressure constantly in respect of both systolic and diastolic BP but azilsartan monotherapy in high dose reduce systolic blood pressure slightly high. Significant change of heart rate was not seen with both the groups.

**Conclusions:** Both the group was effective as well as safe in hypertensive patients.

**Keywords:** Azilsartan, Blood pressure, Chlorthalidone, Heart rate

### **INTRODUCTION**

Hypertension (HTN) exerts a substantial public health burden on cardiovascular health status and is worrisome problem of our healthcare system. Hypertension (HTN) is responsible cause of 57% of stroke and 24% of coronary heart disease deaths in India.<sup>1</sup> The prevalence of hypertension in Indian cities has been steadily increasing from 3.0-4.5% in early 1960's to 11.0 to 15.5% in mid-1990's.<sup>2</sup> Although rural populations in India generally

have lower prevalence of hypertension there has been a significant increase in these populations from less than 1% in early 1960's to 5-7% in late 1990's.<sup>2</sup> An alarming rise in HTN projected by Global Burden of Hypertension 2005 study, the GBD 2010 study and WHO 2011 NCD India specific data portrays a grim picture for the 17.8% of the world's population who reside in India.<sup>3-5</sup> One of the goals of antihypertensive therapy is to bring the overall mean BP down, but also to reduce the daily variability. Eight classes of medications are currently used in the treatment of

hypertension. They include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), calcium-channel blockers (CCB), beta-adrenergic blockers, alpha-adrenergic blockers central alpha-adrenergic receptor agonists and direct renin inhibitors (DRIs). Many of these drugs are available in combination with other antihypertensive agents, such as the aliskiren, the CCB amlodipine, and the thiazide diuretics. The goal for maintaining BP is <130/90mm of Hg according to recent guidelines. According to JNC -8 guideline the four groups ACE, ARB, CCB, Thiazide are the initial choice should be unless and otherwise any contraindication or compelling indication is present.

Azilsartan medoxomil is a newly added to the ARB class of antihypertensive agents. It received FDA approval in February 2011. Azilsartan and chlorthalidone combination got the same in December 2011. Angiotensin II, a peptide hormone, is the principal pressor agent of the renin-angiotensin system (RAS). It is also a potent, direct vasoconstrictor. It stimulates the synthesis and release of aldosterone and thus promotes renal tubular reabsorption of sodium and causes sodium and water retention. As an ARB, azilsartan medoxomil selectively inhibits angiotensin II from binding to the angiotensin II type-1 receptor (AT1). By blocking the action of angiotensin II, azilsartan exerts its antihypertensive effect.

Azilsartan medoxomil is a prodrug, which is hydrolyzed to its active moiety, azilsartan, at the level of the gastrointestinal tract. Azilsartan reaches its peak plasma concentration between 1.5 and 3 hours after administered orally. If it is administered with food, that does not affect its bioavailability, which is approximately 58%.<sup>6</sup> Azilsartan is metabolized in the liver (by O-dealkylation) via cytochrome P450 (CYP) 2C9, resulting in the formation of a nonactive metabolite, M-II.

Serum concentrations of chlorthalidone reaches its peak at approximately 2-6 hours.<sup>7,8</sup> The recommended starting dose of azilsartan/chlorthalidone is 40/12.5mg taken orally once daily. Most of the antihypertensive effect is apparent within 1 to 2 weeks. The recommended starting dose of azilsartan is 80mg. Azilsartan is a safe and effective treatment option for every stage of hypertension, both alone or in fixed-dose combination tablets with chlorthalidone or amlodipine.<sup>9</sup>

## METHODS

It was a prospective observational study. The study was done in medicine Out Patient Department of , Bankura Sammilani Medical College & Hospital, Bankura, West Bengal in rural Bengal for the period of three month from the month of February to month of April in the year 2018. the patients were examined at the starting of therapy, then after 2 weeks, 4 weeks, 8 weeks and 12 weeks respectively for blood pressure and heart rate.

### Inclusion criteria

- Patients greater than 18 years and less than 55 years of age
- Patients of either sex of above criteria.
- Drug naïve patient.
- Patient noncompliance on ACE inhibitor due to adverse reaction
- Patient was on mono-therapy with either ARB or Thiazide and not controlling.

### Exclusion criteria

- Patient of <18 year and >55 year
- Patient was on any antihypertensive mono-therapy other than ARB
- Patient was on combination therapy
- Any comorbid condition
- Pregnant and lactating woman
- Any history of drug allergy of ARB.

Clinic blood pressure (BP) was measured by the physician according to guidelines of the International Society of Hypertension (ISH)/World Health Organisation (WHO) 1999 and the JNC-7.<sup>10</sup> Measurements were taken using a standard mercury sphygmomanometer with appropriate cuff size. Three BP measurements were taken using the subject's right arm with the subject in the sitting position after five minutes of rest, with one minute between measurements. The mean of three measurements were taken as the final value.

Participants with an elevated BP measurement were advised to attend a second visit after one week for measuring their BP again. The average BP of the second visit was used as a criterion for the diagnosis and control of hypertension.

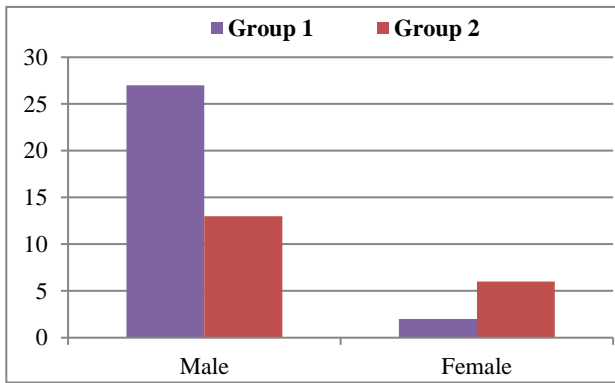
In addition, all treated hypertensive patients were asked to return for a second visit after two weeks and then again as stated above to have their BP measured. Hypertension was defined as systolic blood pressure (SBP)  $\geq 140$  mmHg, diastolic blood pressure (DBP)  $\leq 90$  mm Hg. Then the medicines were given by physician of his choice in two groups azilsartan (80mg) -group 1 and azilsartan 80mg+chlorthalidone 12.5mg -group 2 and the data were putted in a case reporting form after every check-up. Recruitment done on the basis of inclusion and exclusion criteria and the recruitment procedure was done for first three months. Each patient was observed for a period for three months. They were checked on 2<sup>nd</sup>, 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> week.

Then BP of every check-up were distributed in a XL spread-sheet and then analysed by using a Graph-pad prism version 6 software and also SPSS 22 software and ultimately concluded as the lowering of blood pressure in each group. Unpaired t test and Friedman one way ANOVA were used as statistical test. The baseline BP were also analysed.

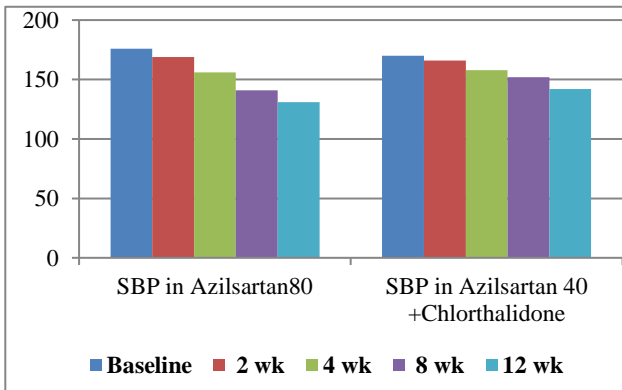
**RESULTS**

The results were obtained by using Graph pad prism and SPSS 22 software and analysed.

Authors found that in azilsartan 80mg group (group 1), mean age was 58.38 year with standard deviation (SD) 13.95 and in azilsartan 40mg plus chlorthalidone 12.5mg group (group 2), mean age was 53.58year and SD was 11.5. In case of height we found mean and SD 165.79cm and 9.08 in group 1 and 161.58cm and 11.95cm in group 2. In case of weight we found in group 1 mean 75.62 kg and SD 10.88 and group 2 mean 66.26kg and SD 11.23. In case of age, height and weight P value was 0.639, 0.094 and 0.829 respectively, those were insignificant. In case of sex distribution, authors found significant P value of 0.045 which clearly shows male preponderance of hypertension (Figure 1).



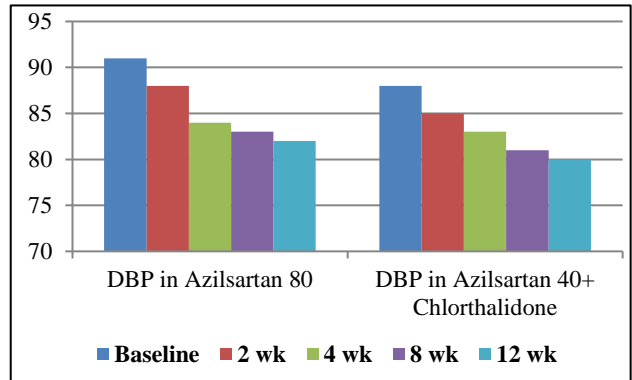
**Figure 1: Sex distribution.**



**Figure 2: SBP changes in two groups.**

Authors analyse the base line systolic (SBP) and diastolic blood pressure (DBP) in two group to see whether there any significance difference or not and found p value 0.0877 in SBP and 0.0612 in DBP, non-significant in both the occasion. The patients were again checked for blood pressure on 2wk, 4wk, 8wk, 12wk and recorded. Authors found in group 1 the significant fall in SBP and also in DBP. In both occasion it was found <0.0001, that is highly sensitive. In case of SBP in group 1 differences between all observations from baseline to 1st visit and consequently in

all the next visits. The mean value was 175.9, 169.2, 155.6, 141.0 and 131.2 subsequently (Figure 2).

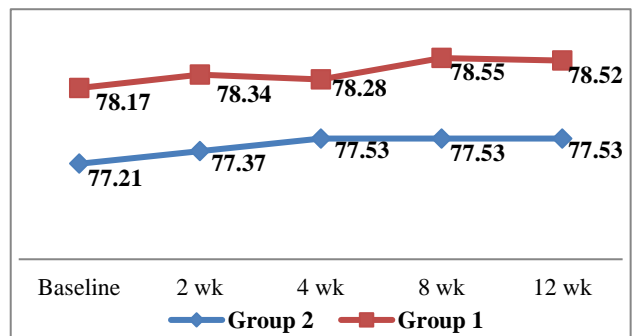


**Figure 3: DBP changes in two groups.**

Mean value in case of SBP change was 9.84, 10.08, 9.86, 8.69, 7.84 in respective visit. In case of DBP of group 1 the mean value was 90.55, 87.59, 84.00, 82.83, 81.17 (Figure 3) and SD was 4.72, 4.42, 4.17, 3.32, 2.80 respectively. So, it is clearly efficacious in reducing both SBP and DBP.

In case of group 2 the p value was insignificant in SBP in first visit and then these were significant <0.001 in all occasions but in case of DBP p value was significant <0.001 in all cases. In case of SBP the mean were 170.42, 165.63, 158.21, 151.28, 142.00 (Figure 2) and SD WERE 11.92, 11.77, 10.11, 9.15, 4.57 in respective visits. In case of DBP the value of mean and SD were 87.79, 85.16, 82.63, 81.05, 80.00 (Figure 3) and 5.12, 6.48, 4.67, 4.78, 3.27. So azilsartan 40mg and chlorthalidone 12.5mg combination is also effective in reducing blood pressure systolic as well as diastolic.

If authors consider in between two group then in case of SBP no significant difference in first two visits but significantly fall in SBP after 8week and 12 weeks in case of azilsartan 80mg than azilsartan 40mg and chlorthalidone 12.5mg, p value 0.0002 in 8wk and <0.0001 in 12 wk. The mean value in group2 and group 1 was 151.48 and 141.03 respectively at 8week and 142 and 131.17 respectively at 12 week. The SD value in group1 and group 2 was 9.15 and 8.69 at 8week and 4.57 and 7.84 at 12 weeks.



**Figure 4: Heart rate changes group-wise and in follow-up.**

Heart rates were also observed in two groups for safety parameter. Authors found that heart rate change was insignificant in p value 0.238 in group 1, but p value is significant 0.017 in case of group 2. When we search for detail into these variations, we found p value in group 2 significant from baseline to 4wk, 8 wk and 12 wk. But the mean was 77.21 at baseline and then 77.37, 77.53, 77.53 and 77.53 in subsequent visits (Figure 4). These all are insignificant clinically.

So, both the group are safe in respect of heart rate.

## DISCUSSION

It is recommended that for many hypertensive patients requiring a >20mmHg decrease in SBP need combined therapy.<sup>10</sup> In the ALLHAT trial, authors have seen 63% of the study population was given two or more drugs; and at the end of 5years only 66% had achieved controlled BP.<sup>11</sup> It is obvious with some newer trials that high rates of patients requiring more than one drug for BP management; example- INVEST (80%), ASCOT-BPLA (78%), and LIFE (88%).<sup>12-14</sup> In present country many patient needed combination drug for controlling high blood pressure and it is very effective to combine drugs to start treatment.

The benefits of combination therapy compared to monotherapy include increased BP control by different mechanisms of action, lowering dose requirements, and fewer adverse events.

Authors have a very small study population and in rural Bengal where patient compliance is a very big issue, authors have found the result a little bit different in current study.

If authors consider in between two group then in case of Systolic BP, no significant difference in first two visits but significantly fall in SBP after 8week and 12week in case of azilsartan 80mg than azilsartan 40mg and chlorthalidone 12.5mg. The mean value in group 2 and group 1 was 151.48 and 141.03 respectively at 8week and 142 and 131.17 respectively at 12 weeks. That we found a greater achievement in azilsartan monotherapy with 80 mg dose in last two visits. But both the group of drugs is very much effective in lowering blood pressure constantly in respect of both systolic and diastolic BP. Authors have also studied if any change of heart rate is occurring and we found that no clinically significant change occurs over the 3 months study period in heart rate in our study.

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