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A comparative study on efficacy of chlorthalidone and azilsartan in confirmed cases of hypertension associated with ace gene polymorphism

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***Abstract*---**The angiotensin-converting enzyme (ACE) gene consists of 26 exons, it is located on chromosome 17 and its polymorphism is a major contributing factor to hypertension. The aim is to compare the efficacy of Chlorthalidone and Azilsartan in newly diagnosed hypertension patients in association with ACE gene polymorphism. The study was conducted in the department of pharmacology, Rama medical college, Kanpur. After doing genetic test and basic investigation, 90 newly diagnosed patients with hypertension

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associated with ACE gene polymorphism were recruited, followed by grouping into two A&B. Group-A(n=45) patients were given Azilsartan 45mg/day and group-B(n=45) patients were given Chlorthalidone 25mg/day for 3 months. Systolic and diastolic blood pressure (SBP& DBP) was measured before and after 3 months of treatment in both groups and they were compared. Three genotypes were found in ACE gene polymorphism-associated hypertension cases such as I/I, I/D and D/D, the severity of hypertension is more in the D/D genotype followed by I/D and I/I genotypes. All three genotypes of both group-A & B had shown a significant mean reduction in SBP& DBP after 3 months of treatment ($p<0.05$) but the mean reduction was high in the I/I genotype followed by the I/D and then D/D genotype. A significant difference in SBP was found in I/I and I/D genotypes of group-A and group B when compared ($p< 0.05$). Allele **"**D" plays a pathogenic role hence means SBP& DBP was more in D/D genotype than I/D and I/I genotype. Azilsartan is more efficacious than Chlorthalidone in terms of blood pressure control.

***Keywords*---**ACE gene, hypertension, Azilsartan, chlorthalidone.

Introduction

According to the guidelines given in 2017 by the American college of cardiology (ACC)/American heart association (AHA), hypertension is defined as systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg (Brook & Rajagopalan, 2018). Patient with CHD, CHF, diabetes mellitus, post renal transplantation and stroke should maintain blood pressure below 130/80 mmHg. Globally hypertension is the major risk factor for cardiovascular events and mortality in adults (Lloyd-Jones et al., 2009; S.S. et al., 2012; Nuthalapati, Ghanta, Natesh, & L.V.K.S., 2021). Risk factors for hypertension are diabetes (15%–20%), lipid disorders (elevated low-density lipoprotein-cholesterol (LDL-C) and triglycerides (30%), overweight-obesity (40%), hyperuricemia (25%) and metabolic syndrome (40%), as well as unhealthy lifestyle habits (eg, smoking, high alcohol intake, sedentary lifestyle). More than 50% of hypertensive patients have additional cardiovascular risk factors (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; Tunstall-Pedoel, Chen, & Kramarz, 2004; Ghanta, Khan, & Bhaskar, 2021).

Angiotensin-converting enzyme (ACE) is a key component of both the renin-angiotensin-aldosterone system (RAAS) and the Kininekallikrein system (Crisan & Carr, 2000). ACE gene maps to chromosome 17q23 spans 21 kb, and comprises 26 exons and 25 introns (Tikhomirova et al., 2017). Polymorphism in intron 16 results in three genotypes insertion homozygote (I/I), insertion/deletion heterozygote (I/D) and deletion homozygote (D/D). The serum ACE levels are determined by the ACE polymorphism in the following order: DD > I/D > II (Choudhury, Jothimalar, & Patra, 2012). Several studies have shown that the DD genotype is associated with a higher risk for myocardial ischemia (MI) and CAD.

The treatment of hypertension includes both non-pharmacological and pharmacological approaches. The choice of approach depends on whether there is

a pre-existing CV, DM, and CKD. If the patient with stage one hypertension and no pre-existing CV, DM, CKD and the risk of cardiovascular disease is less than 10%, the AHA/ACC (American heart association/American College of Cardiology) guidelines suggest lifestyle modifications for 3-6 months alone. AHA/ACC recommends both lifestyle modification and medication for stage-2 hypertension with pre-existing like DM, CKD and 10 years risk of CV event is 10% or high. The non-pharmacological approach includes Dietary Salt Restriction, weight loss, physical activity, moderate alcohol intake, High Fiber and Low-fat Diet and withdrawal of interfering medications. Pharmacological approach initiated with any one of the following four classes: ACE inhibitors (Angiotensin converting enzyme), ARBs (Angiotensin receptors blockers), CCBs (Calcium channel blockers) and thiazide-type of diuretics and each class of antihypertensive drugs reduces CV events (Siragy, 2003). The aim of the present study is to see the efficacy of chlorthalidone and azilsartan in newly diagnosed hypertension patients associated with ace gene polymorphism.

Methods

It is a prospective, open-labelled control clinical trial conducted in the department of pharmacology in collaboration with general medicine, Rama medical college, hospital and research centre, Kanpur. The study was started after getting approval from the institutional ethical committee. As per the following inclusion and exclusion criteria patients were recruited after obtaining informed concerns from each patient.

Inclusion Criteria

- ✓ Patients with hypertension and indicated for treatment with study drugs.
- ✓ Patients were willing to participate in the study.
- ✓ Patients with an age group of 30-50 years from both sexes.

Exclusion criteria

- ✓ Patients were not willing to participate in the study.
- ✓ Smokers/ alcoholics /Pregnant & lactating women.
- ✓ Patients with chronic diseases.
- ✓ Hypersensitivity to any of the study drugs.

Estimation of Blood Pressure

Blood pressure was estimated by an auscultatory method using a sphygmomanometer.

Isolation of DNA

2-3 ml of blood was collected from each patient in an EDTA vial. Genomic DNA was extracted from peripheral blood leukocytes by salting out method using Qiagen Kit (Miller, Dykes, & Polesky, 1988). 1% Agarose gel electrophoresis was used for estimating the quality of DNA and the quality of DNA was also calculated with the use of a standard spectrophotometer at 260 nm and 280nm ratio.

ACE gene polymorphism by polymerase chain reaction

To determine the ACE gene genotype (SNP rs4343) of cases of newly diagnosed hypertensive patients, the genomic DNA fragments were amplified by PCR. Following primers were used to detect gene presence and followed by polymorphism.

Forward Primer: 5'-CTGGAGACCCCCATCCTTTCT-3' Tm=56.00^{o}C
Reverse Primer: 5'-GATGTCGCCATCACATTCGTCAGAT-3' Tm=57.56^{o}C
The PCR conditions were 95^{o}C for 3min, 35 cycles of 95^{o}C for 30s, 52^{o}C for 30s, 72^{o} C for 1.20 min and final extension at 72^{o}C for 5min.

After doing the basic investigations and genetic tests, a total of 90 newly diagnosed hypertension patients were recruited in the present study. ACE gene was detected in all of them. 90 Patients were divided into two groups, group-A and Group-B. Group-A (n=45) patients were given Azilsartan 45mg /OD for 3 months and group-B (n=45) patients were given Chlorthalidone 25mg /OD for 3 months. The present study has 7 visits, each visit was scheduled every 15 days except 1st visit, which is scheduled at just after 7 days. At every visit, each patient was checked for a general medical condition and blood pressure.

Statistical analysis

Data was analyzed by paired t-test and unpaired test analyzed using SPSS software

Results

Table 1
Showing distribution of genotypes among the study population

Genotype	n =90 patients	Percentage
D/D	32	35.55%
I/D	34	37.77%
I/I	24	26.66%

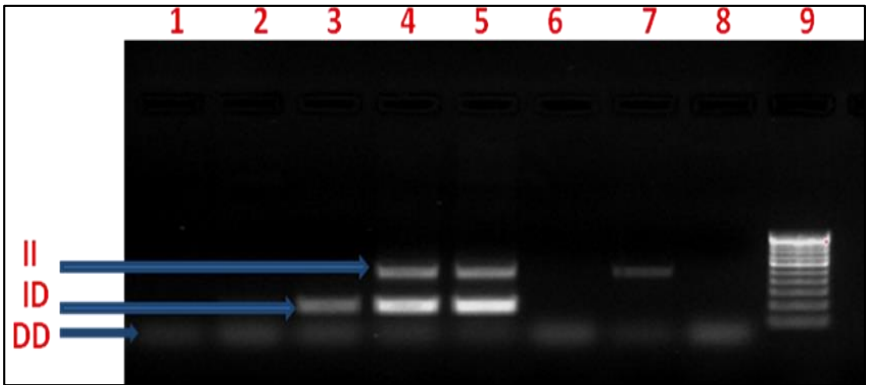

Figure-1: PCR product digested with restriction fragment length polymorphism (RFLP)

The frequency of the D/D allele was 35.55% (32 patients), the I/D allele 37.77% (34 patients) and the I/I allele was 26.66% (24 patients). The frequency of the I/D allele was more as compared with the I/I and D/D allele (Table-1). Three genotypes were found in ACE gene polymorphism those are, II homozygous, ID heterozygous and DD homozygous. II allele was observed at 421bp and ID allele was observed at 200bp and DD band was observed at 50bp (Figure- 1).

Table 2
Age and gender-wise distribution of study population

Variables		n= 90	Percentage
Age group	30 to 40 years	25	27.77
	41 to 50 years	36	40
	51 to 60 years	29	32.22
Gender	Male	51	56.66
	Female	39	43.33

Table 3
Systolic &diastolic blood pressure in ACE gene-positive hypertension patients treated with Azilsartan

Genotype	Variable	Baseline (mean ±SD)	3rd Month (mean ±SD)	Mean difference± SD	p-value
I/I	Systolic blood pressure	162.30±6.36	126.92±4.59	35.38±1.77	P<0.001**
I/D		166.12±4.99	132.25±2.04	33.87±2.95	P<0.001**
D/D		166.28±5.07	134.19±3.89	32.02±1.18	P<0.001**
I/I	Diastolic blood pressure	100.76±5.62	84.76±3.60	16±2.02	P<0.001**
I/D		102.25±3.64	86.25±4.55	16±0.91	P<0.001**
D/D		102.85±4.13	88.38±4.17	14.47±0.04	P<0.001**

Significance=p<0.05**

Table 4
Systolic & Diastolic blood pressure in ACE gene-positive hypertension patients treated with Chlorthalidone

Genotype	Variable	Baseline (mean ±SD)	3rd Month (mean ±SD)	Mean difference± SD	p-value
I/I	Systolic blood pressure	164.33±3.17	134.16±3.24	30.21±0.07	P<0.001**
I/D		168.13±2.77	138.13±2.32	30±0.45	P<0.001**
D/D		168.60±4.80	140.08±2.92	28.52±1.88	P<0.002**
I/I	Diastolic blood pressure	98.50±3.72	84.50±2.11	14±1.61	P<0.001**
I/D		100.13±3.58	88.26±3.84	11.87±0.26	P<0.001**
D/D		100.86±4.70	88.95±4.54	11.91±0.16	P<0.002**

Significance=p<0.05**

Among 90 patients with newly diagnosed hypertension, 51(56.66%) patients were males and 39(43.33%) were females. Age of 36(40%) patients lies between 41-50 years, 29(32.22%) patients belonged to the age range 51-60 years and 25(27.77%) patients belonged from 30 to 40 years (Table-2). Significant reduction in mean systolic and diastolic blood pressure was observed in all three genotypes (I/I, I/D and D/D) of group-A, who were treated with Azilsartan for 3rd month ($p<0.05$) (Table-3). Significant reduction in mean systolic and diastolic blood pressure was observed in all three genotypes (I/I, I/D and D/D) of group B, who were treated with Chlorthalidone for 3rd month ($p<0.05$) (Table-4). After 3 months of treatment, group-A and group B were compared and found a significant difference in mean systolic blood pressure in I/I and I/D genotypes between the groups ($p<0.05$) (Table-5). However, there was no significant difference in mean diastolic blood pressure found between the groups ($p>0.05$) (Table-6).

Table 5
Comparison of Systolic blood pressure in Azilsartan versus Chlorthalidone treated patients

	Genotype	Azilsartan	Chlorthalidone	Mean Difference ± SD	P-value
Baseline	I/I	162.30±6.36	164.33±3.17	-2.02±2.04 (95% CI -6.24 to 2.19)	P>0.331ns
	I/D	166.12±4.99	168.13±2.77	-1.50±1.46 (95% CI -4.50 to 1.48)	P>0.312ns
	D/D	166.28±5.07	168.60±4.80	-1.80±1.48 (95% CI –4.80 to 1.20)	P>0.233ns
3 months	I/I	126.92±4.59	134.16±3.24	-7.24±1.60 (95% CI-10.0 to 3.92)	P<0.02**
	I/D	132.25±2.04	138.13±2.32	-5.8±0.78 (95% CI-7.49 to 4.27)	P<0.02**
	D/D	134.19±3.89	140.08±2.92	-5.89±1.03 (95% CI-7.97 to 3.81)	P>0.06 ns

Significance=$p<0.05$**

Table 6
Comparison of Systolic blood pressure in Azilsartan versus Chlorthalidone treated patients

	Genotype	Azilsartan	Chlorthalidone	Mean Difference ± SD	P-value
Baseline	I/I	100.76±5.62	98.50±3.72	2.26±1.92 (95% CI -1.71 to 6.25)	P>0.251ns
	I/D	102.25±3.64	100.13±3.58	2.11±1.29 (95% CI -0.53 to 4.77)	P>0.114 ns
	D/D	102.85±4.45	100.86±4.70	1.98±1.38 (95% CI -0.80 to 4.18)	P>0.158 ns
3 months	I/I	84.76±3.60	84.50±2.11	0.26±1.19 (95% CI-2.20 to 2.74)	P>0.824 ns
	I/D	86.25±4.55	88.26±3.84	-2.01±1.51 (95% CI-5.12 to 1.08)	P>0.195 ns

	D/D	88.38±4.17	88.95±4.54	-0.57±1.32 (95% CI-3.2 to 2.08)	P>0.665 ns

Significance=p<0.05**

Discussion

Hypertension is an independent risk factor for cardiovascular complications including coronary heart disease, angina pectoris, stroke, ischemia, and atherosclerosis and it is linked with cardiovascular morbidity and mortality (Franklin & Wong, 2013). An estimate by the World Health Organization (WHO) revealed that around 9.4 million deaths occur per year because of hypertension. The majority of study participants in the present study were males i.e.56.66% and female patients were i.e.43.33%, similar results were found in another study (PR, 2014; Xavier, Mathew, Pradeep, & Pais, 2001). However, some studies have reported a relatively higher incidence of hypertension in females than in males (Beg et al., 2014; Tiwari, Kumar, & Kulkarni, 2004). 40% of study subjects belonged to age group 41 -50years, followed by 32.22% belonging to 51 – 60 years and 27.77% belonged to age group 30 -40 years, there was a study in which majority of the study population belonged to age group above 60 years followed by 50 to 59 years which is not similar to present study findings (Liew et al., 2019). In the present study the distribution of I/D (37.77%) genotype was more followed by D/D (35.55%) and I/I genotype (26.66%) similar results were found in previous studies that included North Indian (Jin et al., 2004; Qadar Pasha et al., 2002; Sehajpal, Gupta, Agrawal, & Goel, 2009). The level of systolic and diastolic blood pressure was very high in D/D genotype as compared to I/D and I/I genotype, which is not supported by the previous study (Schelleman et al., 2005). There was a significant reduction of mean SBP and DBP observed in patients treated with Azilsartan& Chlorthalidone after treatment but the mean reduction was more in Azilsartan-treated patients. When both Azilsartan and Chlorthalidone treated groups were compared, a significant difference was observed in SBP of I/I and I/D genotypes (p<0.05) but not in D/D genotype (>0.05).

Conclusion

Mean systolic and diastolic blood pressure was high in the D/D genotype followed by the I/D & I/I genotype and a better prognosis was seen in the I/I genotype followed I/D genotype, which indicates the pathogenic role of the "D" allele and protective role of "I" allele. The present study also concludes that Azilsartan is more efficacious than Chlorthalidone in terms of blood pressure control, but we cannot generalize the findings of the present study because of the limited sample size, patients recruited were belongs same geographical area and it was not a multicentric study.

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