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# A Study of Safety and Efficacy of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Essential Hypertension Patients

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**Abstract** | **Original Research Article**

The prevalence of hypertension is increasing nowadays and treatment of hypertension will result in decreasing the morbidity, mortality and prevent target organ damage. The present study was done to find the efficacy and safety of Angiotensin Converting Enzyme Inhibitors Angiotensin II Receptor blockers in Essential Hypertension patients. Methods: This prospective and analytical study was done in the Essential Hypertension patients attending, Department of General Medicine, Mahatma Gandhi Memorial Hospital, Kakatiya Medical, College, Warangal. A total of n=60 patients were taken with the diagnosis of Essential Hypertension they were divided into two groups. Group I were n=30 (Enalapril) they were given (Tab Enalapril) 5mg OD, and group II n=30 (Tab Losartan) 50mg OD. An overnight (8 hours) fasting blood sample of 10 ml was obtained from the anti-cubital vein under aseptic conditions in a vacutainer. The biochemical parameters were analyzed by semi auto-analyzer. Results: The renal parameters were measured for the group I (Enalapril) at the start of the treatment and during various follow-ups. There was a slight decrease in serum creatinine from the beginning of the study and at the end of 6 months however, the p values were not found to be significant. The values of parameters in group II (Losartan) were recorded in the present study. The values of blood urea decreased slightly at during the period of study however, it was not found to be significant. The values of serum potassium were found to be increased significantly at the end of 6 months. The mean blood pressure parameters were recorded at the beginning of the study and at the end of 6 months the values of systolic blood pressure were found to be less in group II Losartan, however, the values were not found to be significant. The diastolic blood pressure has shown a greater decrease in the Losartan group and the values were found to be significant. Conclusion: The present study shows that there are overall better efficacy and safety profile with Angiotensin receptor blockers as compared to the Angiotensin enzyme converting inhibitors. The overall incidences of adverse effects were minimal with ARBs. However, there were increased serum potassium levels with the patients treated with ARBs.

**Keywords:** Angiotensin Converting Enzyme Inhibitors, Angiotensin II Receptor blockers, Essential Hypertension.



## INTRODUCTION

Hypertension is the most common cardiovascular disease and it has been defined conventionally as blood pressure ≥140/90 mmHg. Arterial pressure is the product of cardiac output and peripheral vascular resistance or the cardiac output or both. The cardiac output may be reduced by drugs that either inhibits myocardial contractility or decrease ventricular filling pressure. Many of the antihypertensive agents act by affecting the adrenergic system, calcium channels, sodium, and water balance [1]. Although many of the clinical trials classify the severity of Hypertension by diastolic blood pressure, the progressive elevation of systolic pressure is similarly predictive of adverse cardiovascular events [2].

Antihypertensive drug therapy has remarkably improved in the last 60 years. Before 1950, hardly any effective and tolerated antihypertensive was available. Veratrum and sodium Thiocyanate could lower blood pressure but they are toxic and difficult to use. The ganglion blockers developed in the 1950s were effective but inconvenient [3]. Reserpine was a breakthrough, but produced mental depression. The therapeutic potential of hydralazine could not be tapped fully because of marked side effects. Guanethidine,

introduced in 1961, was an improvement on ganglion blockers. The anti-hypertensives of 1960-1970s were Methyl Dopa, β- blockers, Thiazide, and high ceiling diuretics and Clonidine. The status of β- blockers, and diuretics was consolidated in 1970 and selective α1 blocker broke new grounds. The anti-hypertensives of 1980-90s are Angiotensin-converting enzyme inhibitors and calcium channel blockers. Angiotensin II receptor antagonists (Losartan) and potassium channel openers (Pinacidil) are a new class of anti-hypertensives [4]. With the development of these drugs delineation of their long term benefits, complications, and understanding of the principles on which to combine them have been given a new thrust.

The ability to reduce levels of Angiotensin –II with orally effective inhibitors of Angiotensin-converting enzyme represents an important advance in the treatment of Hypertension [5]. The Angiotensin-converting enzyme inhibitors appear to confer a special advance in the treatment of hypertensive patients with Diabetes, by slowing the development of diabetic glomerulopathy and also slowing the progression of other forms of chronic renal disease.

Angiotensin II receptor antagonists act by preventing the action of Angiotensin II at receptor level, these agents relaxes the smooth muscle and thereby promotes vasodilatation, increases renal salt and water excretion reduces plasma volume and decreases cellular hypertrophy. Angiotensin II receptor antagonists also theoretically overcome some of the disadvantages of Angiotensin-converting enzyme inhibitors, but also prevent Angiotensin-converting enzyme inhibitors mediated degradation of bradykinin and Substance – P [6]. So two adverse effects of the Angiotensin-converting enzyme inhibitors – cough and Angioedema have not been associated with Angiotensin II receptor blockers.

A variety of therapeutic agents are in use now to lower systemic blood pressure. Though they are potent in reducing blood pressure, most of the drugs produce side effects and many patients are forced to discontinue the therapy. Hence there is a need for evaluating effective anti-hypertensive drugs which have fewer side effects and more acceptability to patients [7]. It is, therefore, thought pertinent to explore the adverse effects related to liver and renal parameters in patients of essential Hypertension on Angiotensin Converting Enzyme Inhibitors and Angiotensin II receptor blockers.

## MATERIAL AND METHODS

This prospective and analytical study was done in the Essential Hypertension patients attending, Department of General Medicine, Mahatma Gandhi Memorial Hospital, Kakatiya Medical, College, Warangal. Prior approval of the study was obtained from the institutional Ethical committee. A total of n=60 patients were taken and followed up for the study. Patients were selected from those who attended the outpatient department of General Medicine with the diagnosis of Essential Hypertension were selected as per the inclusion and exclusion criteria and Hepatic. The patients were divided into two groups. Group I were n=30 (Enalapril) they were given (Tab Enalapril) 5mg OD, and group II n=30 (Tab Losartan) 50mg OD. Inclusion criteria were patients with Essential Hypertension, above n=30 years of age of either sex, those willing to participate in the study voluntarily. Exclusion criteria were Renal failure, Systemic disorders like Diabetes mellitus, Thyroid disorders, Respiratory disorders, Chronic Bronchitis and COPD, Heart disease, prior treatment with anti-hypertensive in last six months, Pregnant and lactating women. A complete history and physical examination of all the patients were done. Blood pressure measurements as per the standard protocol using mercury sphygmomanometer an overnight (8 hours) fasting blood sample of 10 ml was obtained from the anti-cubital vein under aseptic conditions in a vacutainer. The biochemical parameters were analyzed by semi auto-analyzer. The values of parameters obtained were analyzed and recorded by SPSS version 17 software on windows format.

## RESULTS

A total of n=30 patients included in the Group I were analyzed for liver parameters which included serum alkaline phosphatase (ALP), Aspartate aminotransferase (AST) IU/L, Alanine Aminotransferase (ALT) and Total Serum Bilirubin. The serum alkaline phosphatase levels were found to be decreasing from the beginning of therapy at the end of 6 months the values were found to be significant. The AST levels were also found to be decreasing the p values were not found to be significant. Similarly, the ALT levels were found to be decreasing but not to significant levels. The Total Serum Bilirubin levels were not changed significantly from the beginning of the study to the end of the study given in table 1.

**Table-1: Liver Parameters over a period of six months In Essential Hypertensive Patients on Angiotensin Converting Enzyme Inhibitor (Enalapril)**

| PARAMETER | DURATION OF THE STUDY | | | | % Change | p-Value |
|---|---|---|---|---|---|---|
| | 0 | 1 | 3 | 6 | | |
| **Serum Alkaline Phosphatase (ALP) (IU/L)** | 12.5 ±3.5 | 11 ±3.8 | 10.9 ±2.4 | 9.75 ±3.1 | 8.21 | <0.05* S |
| **Aspartate Aminotransferase (AST) (IU/L)** | 18.9 ±5.1 | 16.9 ±4.3 | 17.1 ±2.77 | 16.9 ±3.23 | 9.75 | 0.1 NS |
| **Alanine Aminotransferase (ALT) (IU/L)** | 17.9 ±5.1 | 14.5 ±5.0 | 13.9 ±3.5 | 15.5 ±2.9 | 14.34 | 0.5 NS |
| **Total Serum Bilirubin (mg/dl)** | 0.69 ±0.14 | 0.65 ±0.12 | 0.63 ±0.12 | 0.58 ±0.12 | 18.96 | 0.5 NS |

The Liver parameters in the group II patients were recorded at the starting of the study and at the end of 1 month, 3 months and 6 months. The ALT levels were found to be decreasing significantly at the end of 6 months the p values were found to be <0.001. Similarly, the ALP levels were found to be decreasing with p values found to be significant. The serum bilirubin levels were not found to be significant shown in table 2.

**Table-2: Liver Parameters over a period of six months in Essential Hypertensive Patients on Angiotensin II Receptor Blocker (Losartan)**

| PARAMETER | DURATION OF THE STUDY | | | | % Change | p-Value |
|---|---|---|---|---|---|---|
| | 0 | 1 | 3 | 6 | | |
| **Serum Alkaline Phosphatase (IU/L)** | 12.8 ± 3.24 | 11.7 ± 3.3 | 11.4 ± 2.9 | 11.8 ± 2.6 | 5.61 | 0.5 NS |
| **Aspartate Aminotransferase (AST) (IU/L)** | 21.87 ± 8.31 | 20.4 ± 6.5 | 19.40 ± 5.2 | 20.15 ± 3.42 | 8.00 | 0.5 NS |
| **Alanine Aminotransferase (ALT) (IU/L)** | 19.95 ± 8.24 | 15.31 ± 6.19 | 12.57 ± 0.13 | 18.47 ± 2.96 | 9.54 | 0.1 NS |
| **Total Serum Bilirubin (mg/dl)** | 0.64 ± 0.13 | 0.61 ± 0.14 | 0.61 ± 0.11 | 0.59 ± 0.11 | 8.48 | 0.1 NS |

The renal parameters were measured for the group I (Enalapril) at the start of the treatment and during various follow-ups. There was a slight decrease in serum creatinine from the beginning of the study and at the end of 6 months however, the p values were not found to be significant. Similarly, the serum sodium levels and potassium levels were measured however the values did not show significant changes at the end of the study given in table 3.

**Table-3: Renal Parameters over a period of six months in Essential Hypertension Patients in Angiotensin Converting Enzyme Inhibitor (Enalapril)**

| PARAMETER | DURATION OF THE STUDY(MONTHS) | | | | % Change | p-VALUE |
|---|---|---|---|---|---|---|
| | 0 | 1 | 3 | 6 | | |
| **Blood Urea (mg/dl)** | 26.04±4.5 | 26.2 ± 4.6 | 25.9 ± 3.9 | 26.76 ± 3.9 | 2.77 | 0.4 NS |
| **Serum Creatinine (mg/dl)** | 0.75 ± 0.2 | 0.67 ± 0.12 | 0.7 ± 0.15 | 0.72 ± 0.19 | -4 | 0.66 NS |
| **Serum Sodium (mEq/L)** | 138.5 ± 3.1 | 139.1 ± 2.8 | 139.9 ± 2.1 | 140.6 ± 2.9 | 3.22 | 0.1 NS |
| **Serum Potassium (mEq/L)** | 3.9 ± 0.5 | 4.0 ± 0.6 | 4.11 ± 0.33 | 4.08 ± 0.25 | 8.5 | 0.4 NS |

The values of parameters in group II (Losartan) were recorded in the present study. The values of blood urea decreased slightly at during the period of study however, it was not found to be significant. The values of serum potassium were found to be increased significantly at the end of 6 months shown in table 4.

**Table-4: Renal Parameters over a period of six months in Essential Hypertensive Patients on Angiotensin II Receptor Blocker (Losartan)**

| PARAMETER | DURATION OF THE STUDY (MONTHS) | | | | % Change | P VALUE |
|---|---|---|---|---|---|---|
| | 0 | 1 | 3 | 6 | | |
| **Blood Urea (mg/dl)** | 27.5 ± 4.71 | 27.25 ± 3.22 | 26.8 ± 2.98 | 26.75 ± 2.8 | -2.73 | 0.35 NS |
| **Serum Creatinine (mg/dl)** | 0.74 ± 0.22 | 0.73 ± 0.19 | 0.74 ± 0.19 | 0.78 ± 0.19 | 5.4 | 0.55 NS |
| **Serum Sodium (mEq/L)** | 142.5 ± 4.3 | 141.1 ± 3.8 | 140.9 ± 4.1 | 138.6 ± 2.7 | 5.25 | >0.1 NS |
| **Serum Potassium (mEq/L)** | 4.0 ± 0.5 | 4.2 ± 0.6 | 4.5 ± 0.33 | 4.8 ± 0.25 | 28.5 | < 0.05 * |

The mean blood pressure parameters were recorded at the beginning of the study and at the end of 6 months the values of systolic blood pressure were found to be less in group II Losartan, however, the values were not found to be significant. The diastolic blood pressure has shown a greater decrease in the losartan group and the values were found to be significant. Similarly, the mean arterial pressure was found to lesser in Losartan group and the p values were found to significant the parameters are shown in table 5.

**Table-5: Showing the reading of mean blood pressure parameters at the end of 1 & 6 months**

| Blood Pressure Parameters | Group I (Enalapril) | | p values | Group II (Losartan) | | p values |
|---|---|---|---|---|---|---|
| | *At the start* | *6 months* | | *At Start* | *6 months* | |
| **Systolic Blood Pressure mmHg** | 145.5 ± 10.5 | 135.50 ± 8.5 | 0.12 | 142.33 ± 9.5 | 131.2 ± 5.6 | 0.235 NS |
| **Diastolic Blood Pressure mmHg** | 96.3 ± 4.5 | 88.56 ± 4.4 | 0.5 | 95.4 ± 4.6 | 84.4 ± 3.4 | 0.05* |
| **Mean Arterial Pressure mmHg** | 110.2 ± 8.5 | 103.66 ± 3.2 | 0.05* | 108.55 ± 6.4 | 100.5 ± 2.4 | 0.02* |

* Significant

Incidence of adverse effects also has been studied in the present study wherein only 8 of 30 patients of group I complained of Headache, nausea, dry cough and none were made by group II patients. The treatment is continued despite the mild side effects mentioned, for six months and all the mentioned side effects subsided after long term use of ACE inhibitors(for six months).

## DISCUSSION

In the present study, n=60 patients of essential hypertension were chosen as subjects, excluding other disease status. The study was conducted for a period of nine months. High blood pressure is an important risk factor for cardiovascular disease. Treatment or control of hypertension is therefore important to reduce death or hospitalization from cardiovascular disease [8]. The renin-angiotensin-aldosterone system is a major regulator of cardiovascular functions; blockade of RAS activity has shown beneficial effects on cardiovascular functions [9]. The use of ARBs or ACE-I as the first line agents for essential hypertension for all populations with CKD is recommended by Eighth Joint (US) National Committee (JNC-8) [10]. The European Society of Cardiology guidelines on diabetes, pre-diabetes and CV disease also recommend ACE-I or ARBs for the person with diabetes or hypertension with coronary artery disease. The present showed that there increase in ALP, in the group I patients after 6 months of treatment with ACE-I however the bilirubin concentration was not found to be increased significantly at the end of treatment. This signifies that there is slight hepatotoxicity with ACE-I treatment. Hagley MT *et al*. [11] have reported hepatotoxicity with Enalapril use and the hepatotoxicity was of cholestatic type. The potential mechanisms of injury included idiopathic hypersensitivity and modulation of eicosanoid metabolism by inhibition of Kininase II leading to increased hepatic bradykinin activity. In the present study, we found a slight increase in ALP levels in group I signifying the drug-induced hepatotoxicity. The similar results were not found in the Group II receiving ARBs probably indicating low levels of hepatotoxicity with this drug and no mild elevations of liver enzymes by Losartan does not require dose modifications. The average values of systolic blood pressure decreased in group I and group II, however, the p values were not found to be significant. A similar comparison of DBP in both the group shows the values of DBP decreased to lower levels in the group II and the p values were found to be significant. The recent meta-analysis by Cheng *et al*. [12] showed that ACEI or ARBs had different effects on CV outcomes in patients with DM. And the meta-analysis by van Vark *et al*. [13] showed that ACE-I or ARBs had different effects on all-cause mortality in patients with hypertension. But there is no meta-analysis focused on the comparison of ACEI and ARBs on CV risk in hypertensive patients with T2DM. Other studies have shown that there was no significant decrease in the incidence of major CV events and MI in patients with DM with the use of ARBs. A meta-analysis by Xiaodan lV *et al.* [14] has shown that ARBs did not significantly affect the occurrence of MI, stroke, and CV. The reduction of HF was by 19% had no statistical significance. The present study a better by definite reduction of blood pressure by ARBs and the incidence of side effects were minimal with the use of ARBs as compared to the ACE inhibitors.

## CONCLUSION

The present study has shown that there are overall better efficacy and safety profile with Angiotensin receptor blockers as compared to the Angiotensin-converting inhibitors. The overall incidences of adverse effects were minimal with ARBs. However, there were increased serum potassium levels with the patients treated with ARBs.

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