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COMPARISON OF THE EFFICACY AND TOLERABILITY OF LOSARTAN AND ENALAPRIL IN PATIENTS OF MILD TO MODERATE ESSENTIAL HYPERTENSION IN A TERTIARY CARE HOSPITAL

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ABSTRACT **Background:** Clinical benefits of Angiotensin II receptor blockers (ARBs) outscore angiotensin-converting enzyme inhibitors . The relative advantage of angiotensin II receptor blockers (ARBs) over angiotensin-converting enzyme (ACE) inhibitors for lowering blood pressure in essential hypertension is not clear.

Objective: To compare the efficacy and tolerability of losartan with enalapril in patients of mild to moderate essential hypertension.

Materials and Methods: Patients of mild to moderate hypertension were randomly divided to receive either losartan 50 mg or enalapril 10 mg once a day orally for 12 weeks.

Systolic blood pressure (BP), diastolic BP and pulse rate of each patient were recorded at every consultation. Baseline Investigations such as complete blood count, serum creatinine, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase (ALT, AST), random blood glucose and routine urine examination were performed for baseline reference and after 12 weeks of drug therapy.

Results: The systolic BP in the losartan/enalapril group showed mean reduction of $25.59 \pm 16.30/25.14 \pm 15.50$ mmHg while the diastolic BP in the losartan/enalapril group showed mean reduction of $15.3 \pm 8.36/10.58 \pm 6.05$ mmHg, respectively, at 12 weeks. On comparison of reduction in systolic BP in the two groups, there was no significant difference between the groups ($P > 0.05$). Though the diastolic BP showed greater mean reduction with losartan at 12 weeks ($P < 0.001$) compared with enalapril for the same duration. The incidence of dry cough was higher in enalapril group as compared to losartan group (16% vs. 0%, respectively; $P < 0.05$).

Conclusion: Losartan causes a greater reduction in diastolic BP than enalapril but does not cause dry cough as seen with enalapril.

KEYWORDS : Systolic BP, enalapril, losartan, , hypertension, diastolic BP, blood pressure

INTRODUCTION

Hypertension is often a chronic, age-related lifetime disorder, which usually leads to cardiovascular and renal complications. The onset of essential hypertension is due to inability of the kidney to excrete sodium at a normal range of blood pressure. This can be either primary or secondary in onset. The renin-angiotensin system has a permissive role in the development of essential hypertension.

At present, two main groups of drugs that regulate the renin-angiotensin system and reduce systemic hypertension are available. The two drug groups are angiotensin-converting enzyme (ACE) inhibitors and angiotensin- II receptor blockers (ARBs). The ACE inhibitors reduce the synthesis of angiotensin -II by inhibiting the action of ACE on angiotensin- I .However, the ACE inhibitors do not block the alternative ACE- independent angiotensin -II generating pathways. On the other hand, ARBs block the AT-1 receptors which also decreases the effect of angiotensin -II generated by alternative ACE-independent pathways.

At present, ARBs are used in place of ACE inhibitors for the treatment of essential hypertension when unacceptable adverse effects arise due to ACE inhibitors.

Though the ACE inhibitors and ARBs effectively lower blood pressure, differences in their mechanisms of action and effects underline the need for research on their comparative benefits and risks.[1]

The present study was done to assess the impact of mechanistic properties of ACE inhibitors and ARBs in for better patient compliance and treatment outcomes in mild to moderate essential hypertension .

The ARB, losartan and ACE inhibitor, enalapril, were used in the present study.

MATERIALS AND METHODS

The study was conducted in the Out-Patient Department of Medicine, SNMC Agra, after the approval of the Institutional Ethics Committee. This was an open, randomized, prospective, comparative, controlled clinical trial.

Total of 50 patients were included in the study as per the inclusion criteria. It includes newly diagnosed male and female patients with mild to moderate essential hypertension in the age group of 18–60 years were included in the study. Patients having discontinued antihypertensive therapy for more than 4 weeks were also included .

The exclusion criteria comprised patients on any other antihypertensive therapy, patients allergic to study drugs, patients of secondary hypertension, patients with deranged liver function test (SGOT or SGPT >2 times) , patients with deranged kidney function test (serum creatinine >2 mg/dl), pregnant and lactating females and female patients of the child-bearing age group not using any family planning method.

The patients were included in the study after taking informed and written consent according to selection criteria. Complete medical history was taken during the first visit. Patients were randomly assigned to receive either losartan or enalapril, with 25 patients in each group. Group 1 patients received 50 mg of losartan once a day orally for 12 weeks while group 2 patients received 10 mg of enalapril once a day orally for 12 weeks.

After inclusion into the study, follow-up of patients was done at 2 weeks, 4 weeks, 8 weeks and 12 weeks. Systolic and diastolic blood pressure (BP) were recorded using a mercury sphygmomanometer with auscultatory method along with clinical examination of each patient on every visit. The BP was measured in a sitting position after 10 minutes of rest. Systolic pressure was taken as the first Korotkoff sound and the diastolic pressure coincided with disappearance of sounds. Pulse rate was also noted every time.

Baseline parameters like complete blood count, serum creatinine, AST, ALT, random blood glucose and urine examination were done during the first and last visit.

The primary end point of drug efficacy was the change in diastolic BP from baseline recording in sitting posture. Secondary end point was the change in systolic BP from baseline. Patients who dropped out of the study were not included in final statistical analysis. Drug safety was based on both subjective and objective systemic side-effects. Subjective side effects included nausea, headache, drowsiness, fatigue, body ache, dyspepsia, itch and dry cough which the patient told at each visit. Objective side effects included rash and hypotension

Data were analyzed using Z test. A *P*-value <0.05 was taken as significant, while *P* >0.05 was considered as insignificant.

RESULTS

The patients receiving losartan and enalapril were similar w.r.t. systolic BP, diastolic BP and pulse rate before treatment.

In the losartan group, the mean systolic BP before treatment was 150.42 ± 11.82 mmHg. On administering losartan , the systolic BP decreased to 139.16 ± 9.93 mmHg, 135.13 ± 9.7 mmHg, 128.14 ± 8.69 mmHg and 124.83 ± 8.05 mmHg at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment. This reduction in systolic BP was statistically significant ($P < 0.001$) at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment when compared with the baseline values .

The mean diastolic BP at baseline in losartan group was 96.52 ± 3.06 mmHg. After treatment, the diastolic BP reduced to 88.45 ± 1.53 mmHg, 86.24 ± 2.32 mmHg, 83.26 ± 3.57 mmHg and 81.22 ± 3.66 mmHg at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment. The reduction in diastolic BP was statistically significant ($P < 0.001$) at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment when compared with the baseline values.

In the enalapril group, the mean systolic BP before treatment was 155.65 ± 9.86 mmHg. After treatment, the systolic BP reduced to 141.5 ± 15.74 mmHg, 139.62 ± 10.12 mmHg, 134.87 ± 9.13 mmHg and 130.51 ± 8.24 mmHg at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment. The reduction in the mean systolic BP was found to be statistically significant ($P < 0.001$) at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment when compared with the baseline readings values.

The mean diastolic BP before treatment in enalapril group was 97.64 ± 3.96 mmHg. After treatment, the diastolic BP decreased to 90.72 ± 1.56 mmHg, 88.07 ± 1.32 mmHg, 87.68 ± 1.98 mmHg and 87.06 ± 1.28 mmHg at 2 weeks, 4 weeks, 8 weeks and 12 weeks, respectively. The decrease in the diastolic BP with enalapril was found to be statistically significant ($P < 0.001$) at 2 weeks, 4 weeks, 8 weeks and 12 weeks of treatment when compared with the baseline values.

The mean reduction in systolic BP in the losartan/enalapril group was 11.26 ± 12.28/14.15 ± 14.92 mmHg, 15.29± 13.24/16.03 ± 12.80 mmHg, 22.28 ± 15.22/20.78 ± 14.08 mmHg and 25.59 ± 16.30/25.14 ± 15.50 mmHg, respectively, at 2 weeks, 4 weeks, 8 weeks and 12 weeks. There was no significant difference between the groups ($P > 0.05$) when decrement in systolic BP was compared.

The mean reduction in diastolic BP in the losartan/ enalapril group was 8.07 ± 4.68/6.92 ± 4.58 mmHg and 10.28 ± 5.81/9.57 ± 5.61 mmHg, respectively, at 2 weeks and 4 weeks. There was no statistical difference between the two groups when the values were compared ($P >0.05$). The mean reduction in diastolic BP in the losartan/enalapril groups at 8 weeks and 12 weeks was 13.26 ±7.42/9.96 ± 5.88 mmHg and 15.3 ± 8.36/10.58 ± 6.05 mmHg, respectively**.** The mean decrease in diastolic BP achieved with losartan at 8 weeks and 12 weeks was significantly higher ($P < 0.001$) than enalapril for the same period of treatment.

The adverse effects were studied in all patients who completed the study. A total of 8% of the patients reported one or the other adverse-effects like fatigue (4%) and headache (4%) in the losartan group. In the enalapril group, adverse effects were seen in 24% of patients like fatigue (4%), headache (4%) and dry cough (16%). However, no statistical significance was noted in the frequency of adverse effects between the two treatment groups. ($P > 0.05$).

In the enalapril group, dry cough as an adverse effect was seen in 16% patients while it was 0% in the losartan-treated group. When both the groups were compared, dry cough was significantly associated with enalapril group than losartan group ($P < 0.05$).

Table 1: Comparative effect of losartan and enalapril on systolic blood pressure

Paramaters	Losartan systolic BP in mm Hg (mean± SD)	Enalapril systolic BP in mm Hg (mean± SD)	p-value
Baseline	150.42 ± 11.82	155.65 ± 9.86	> 0.05
After 2 weeks	139.16 ± 9.93	141.5 ± 15.74	> 0.05
After 4 weeks	135.13 ± 9.7	139.62 ± 10.12	> 0.05
After 8 weeks	128.14 ± 8.69	134.87 ± 9.13	> 0.05
After 12 weeks	124.83 ± 8.05	130.51 ± 8.24	> 0.05

Table 2: Comparative effect of losartan and enalapril on diastolic blood pressure

Paramaters	Losartan diastolic BP in mm Hg (mean± SD)	Enalapril diastolic BP in mm Hg (mean± SD)	p-value
Baseline	96.52 ± 3.06	97.64 ± 3.96	> 0.05
After 2 weeks	88.45 ± 1.53	90.72 ± 1.56	> 0.05
After 4 weeks	86.24 ± 2.32	88.07 ± 1.32	> 0.05
After 8 weeks	83.26 ± 3.57	87.68 ± 1.98	< 0.001
After 12 weeks	81.22 ± 3.66	87.06 ± 1.28	< 0.001

DISCUSSION

The renin- angiotensin system is a key ingredient in the maintenance of blood pressure. Angiotensin –II is the chief chemical entity of this system which acts on AT1 and AT2 receptors. Angiotensin II is a major regulator of not only fluid and sodium balance but also of cellular growth and remodeling of cardiovascular system. Angiotensin II exerts its actions via AT1 and AT2 receptors which broadly mediate opposite functions. AT1 receptors have potentially harmful consequences, if not properly counterbalanced. AT1 receptors are concerned with vasoconstriction, thirst and release of vasopressin and aldosterone, fibrosis, cellular growth, migration and atherosclerosis and vascular ageing. AT2 receptors concern with protective actions like vasodilation, release of nitric oxide (NO) and inhibition of cell growth.

ACE inhibitors reduce the synthesis of Angiotenin-II and ARBs block the AT1 receptors but the comparative efficacy of ACE inhibitors and ARBs is a talking point. The AT1 receptor can still be activated by Angiotensin-II when ACE inhibitors are used which is due to the possible generation of Angiotensin-II by alternate pathways . The same AT1 receptor is more effectively blocked by ARBs which are able to take care of the Angiotensin-II generated by alternate pathways. Thus this study was performed to compare the efficacy of ACE inhibitors and ARBs in patients of essential hypertension.

As a commonly used ACE inhibitor enalapril was used on a set of patients of essential hypertension for comparison with losartan which shows competitive insurmountable antagonism at AT1 receptors. Insurmountable antagonism leads to sustained receptor blockade even with increased levels of endogenous ligand and with missed doses of drug.

Losartan potassium is an orally active, nonpeptide angiotensin II (AII) receptor antagonist. It is the first of a new class of drugs to be introduced for clinical use in hypertension. This novel agent binds competitively and selectively to the AT_1 receptor, thereby blocking Angiotenin-II-induced physiological effects. An active metabolite, E3174, contributes substantially to its antihypertensive effect, which persists throughout 24 hours after once-daily administration.[2]

The two groups were comparable to each other in terms of age, body-weight and baseline characteristics like gender distribution and personal habits(tobacco and alcohol consumption).

In the present study 20% patients in the enalapril group and 28% patients in the losartan group were on some or the other antihypertensive medication. These patients had discontinued their medication for a period of more than 4 weeks . So they were enrolled in the study.

In the present study it was observed that both losartan and enalapril are effective in reduction of systolic and diastolic BP alike. This was noted through the study period spanning 12 weeks. On comparison of the efficacy of losartan with enalapril, it was observed that losartan is more effective than enalapril in reducing diastolic BP . Although reduction in systolic BP is almost similar for both losartan and enalapril.

The findings of the present study are similar to that of another double blind, controlled, parallel and multicentric study where losartan potassium reduced the DBP to < 90 mm Hg in 59% of the patients at the end of 8 weeks compared to 45% in the enalapril maleate group. DBP was reduced by 10 or > than 10 mm Hg in 89% of the patients with losartan as compared to the baseline whereas it was 80% in the enalapril group.[3]

In another study losartan potassium lowered the DBP to <90 mmHg in 62% of the patients at the end of 8 weeks compared to 40% in the enalapril group.[4]

The better effect of losartan at reducing diastolic BP than enalapril could be due to the blockade of the AT1 receptors by ARBs. This takes care of the Angiotensin-II synthesized by alternate pathways. ACE inhibitors like enalapril are not able to block the effects of Angiotensin –II synthesized by non-ACE pathways.

The ARBs decrease both systolic and diastolic BP just like ACE inhibitors . However decrease in diastolic BP is seen more in our study . This can be due to the effect of 5-carboxylic acid metabolite, EXP 3174, which is more potent than losartan as an AT1 receptor antagonist and has a longer $t_{1/2}$ than the drug itself. A similar greater decrement in diastolic BP with telmisartan as compared to enalapril was seen with another study.[5] No serious side effects were seen with the use of either drug. The side effect seen with losartan were fatigue and headache. In the enalapril group the side effects seen were fatigue , headache and dry cough .Dry cough as a side effect was seen with only enalapril. None of the side effects resulted in discontinuation of the drug.

No major adverse effect was seen on any biochemical parameter. This shows the good safety profile of the drugs.

Thus it can be suumarized that both losartan and enalapril cause a significant fall in BP . However, the reduction in diastolic BP is more by losartan. At the same time losartan does not cause dry cough which is seen with enalapril.

Thus because of its safety profile and better tolerability losartan could be preferred as a first line drug among ARBs for the treatment of mild to moderate essential hypertension.

Losartan causes a greater decrease in diastolic BP as compared with enalapril . The greater benefit of antihypertensive agents in lowering diastolic BP is still a matter of debate. This is because reduction in systolic BP is associated with better cardiovascular outcomes. Thus, further studies are needed to study the effect of antihypertensive agents on diastolic BP and its effect on cardiovascular health.

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