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Original Article

Pharmacology Section

Pleiotropic Effects of Losartan in Hypertensive Patients with Dyslipidemia

SIVAKUMAR SIVASUBRAMANIAM[1], BANUPRIYA KUMARASAMY[2]

ABSTRACT

Introduction: In essential hypertension, the comorbidity of dyslipidemia is very common. In addition to hypertension, dyslipidemia is linked to cardiovascular disease, stroke and decline in renal function. Unlike other angiotensin receptor blockers, Losartan has been claimed to have unique pleiotropic property and thereby decreasing the risk of future cardiovascular complications.

Aim: The present study was done to assess on the pleiotropic effect of losartan in newly diagnosed hypertensive patients with dyslipidemia.

Materials and Methods: Fifty four hypertensive patients with dyslipidemia who fulfilled the eligible criteria and were willing to give informed consent were included in the study after getting Institutional Ethical Committee (IEC) approval. All the study participants were given tab. Losartan 50mg once daily for four weeks. At the end of 1st, 2nd, 3rd and 4th week, blood pressure control and compliance were monitored. At the end of 4th week all the baseline laboratory parameters like renal function test, liver function test, lipid prolife and random blood sugar were performed. The EQ-5D questionnaires were completed at two points during the study: at the patient's initial visit before enrollment in the study and after 4 weeks of Losartan therapy. Appropriate statistical methods were used to analyse the results.

The primary endpoint was reduction in blood pressure and improvement in lipid profile and improvement in quality of life score from baseline after 4 weeks of losartan therapy

Results: Four patients were withdrawn due to non-compliance and totally 50 patients completed the study. The mean systolic blood pressure was reduced from 154.54 mm Hg to 138.16 mm Hg with $p<0.0001$ and the mean diastolic blood pressure was reduced from 91.56 mm Hg to 82.44 mm Hg with $p<0.0001$. There was a significant reduction in the mean total cholesterol from 189.52 to 180.46 mg/dl, mean LDL from 110.50 to 101.32 mg/dl and mean triglygeride from 135.68 to 127.70 mg/dl with $p<0.0001$. Improvements in anxiety and depression, as well as other dimensions in the QOL questionnaire, paralleled with improvement of the clinical picture.

Conclusion: Based on the results of this study, Losartan is safe and effective in treating hypertensive patients with dyslipidemia in addition to its antihypertensive effect and it also has benefits of reducing serum glucose, lipid levels; and improvement in the quality of life.

Keywords: Dyslipidemia, Hypertension, Losartan

INTRODUCTION

Hypertension is a worldwide epidemic defined as Blood pressure in excess of 140/90mmHg. According to the WHO 2008 estimates, the prevalence of hypertension in Indians was 32.5% (33.2% in men and 31.7% in women) [1]. According to the ICMR survey report, the prevalence of hypertension varied from 17-21% in all the states with marginal rural urban differences [2]. Genetic factor, foetal factor and environmental factors like alcohol, obesity, sodium intake, insulin resistance, stress and humoral mechanism contribute to the etiology of hypertension [3].

Hypertension has earned the designation as "silent killer" because it typically has no symptoms, but it causes progressive harm to cardiovascular system [4]. When blood pushes with too much force through cardiovascular system, it can damage the walls of the arteries as well as heart muscle. It eventually contributes to a heart attack. Similarly, damage to the arteries that supply blood to the brain can contribute to a stroke and damage to the arteries that supply blood to the kidneys can lead to kidney disease [4]. The goal of antihypertensive treatment is to decrease the cardiovascular risk of the patients by treating associated diseases and possible hypertensive end organ damages [5].

According to JNC-8 guidelines, Renin-angiotensin-aldosterone System (RAAS) blockade will be recommended as the new first-line therapy for the treatment of hypertension especially in high-risk patients like those with the metabolic syndrome, and those with high cardiovascular risk based on family history and other typical risk factors, so losartan can be given as initial therapy for newly diagnosed hypertensive patients less than 55-year-old [6]. In contrast to other angiotensin II antagonists, Losartan has unique pleiotropic uricosuric and lipid lowering property and thereby reducing the risk of future cardiovascular complications in hypertensive patients [7].

Risk factors such as obesity, hyperlipidemia and hyperglycemia should be considered in the assessment of overall cardiovascular risk [7]. The present study was done to assess the pleiotropic effect of losartan in newly diagnosed hypertensive patients with dyslipidemia.

MATERIALS AND METHODS

This Interventional, open label, prospective clinical study was done at Hypertension Out Patient Department of Tirunelveli medical college during the period of July 2016 to February 2017(8 months) in 54 hypertensive patients with dyslipidemia who were given tab Losartan 50 mg for 4 weeks. Among 54 patients, 4 patients were withdrawn from the study due to non-compliance and 50 patients who completed the study were taken for statistical analysis.

Approval from Institutional Ethical Committee of Tirunelveli Medical College Hospital was obtained, before starting the study. Written

informed consent was obtained in local vernacular language from every patient before enrollment.

Newly diagnosed patients of stage 1 and stage 2 essential hypertension (Stage 1 hypertension with SBP 140-159(mmHg) or DBP 90-99(mmHg) and stage 2 hypertension with SBP≥160 (mmHg) or DBP≥100(mmHg) according to JNC 7 adult classification), both male and female, age>18-year-old and <60-year-old, LDL >100mg/dl, TG >150mg/dl and HDL <400mg/dl were included in the study.

Patients with secondary hypertension, hypertensive patients on antihypertensive drugs, patients with Hepatic disease, history of gout and renal lithiasis within the last two years, patients with myocardial infarction, angina and heart failure within the last 3 months, pregnancy and lactation, those with history of allergic reactions to study drugs, age <18-year-old and >60-year-old and history of neurologic or mental disorders were excluded from the study.

Withdrawal Criteria

Blood pressure ≥ 180/110 mmHg, protocol deviation, request for withdrawal by the subject, non-compliance with protocol and adverse effects (decision about withdrawal from the study was made either by investigator or subject).

Schedule of Study Visit

a) Screening and recruitment:

During enrollment clinical assessment and the following baseline investigations were done.

- Demographic data of patients were recorded.
- Blood pressure measurement was done for all patients in seated position after 10 minutes of rest.
- Liver function tests (SGOT, SGPT, Total Bilirubin and ALP), random blood sugar, lipid profile(total cholesterol, LDL, total triglyceride) and renal function tests (serum creatinine, blood urea, serum potassium and sodium) were done in a random blood sample of 2 ml using automated analyser.
- EuroQol Group's EQ-5D questionnaire was used to measure the quality of life of all patients [8]. The EQ-5D quality of life questionnaires were self-administered and respondents completed them while in the hypertension OPD. The EQ-5D index scale included five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had three levels: no problems, some/moderate problems and severe problems with the score of 1, 2 and 3 respectively.

b) Treatment protocol:

The patients received tab. Losartan 50mg every morning once daily orally for duration of four weeks before meal. Medication compliance was measured by pill count method.

Follow Up

At the end of 1st, 2nd, 3rd and 4th week blood pressure control, tolerance and compliance were monitored. Patients were instructed to report to the outpatient department at the end of every week with the diary to access the tolerance and at the end of second week along with empty strips to collect the drugs. At the end of 4th week all the baseline laboratory parameters like renal function test, liver function test, lipid prolife and random blood sugar were performed. The EQ-5D questionnaires were completed at two points of time: at the patient's first visit before enrollment in the study and after 4 weeks of Losartan therapy.

Primary Endpoint

- Changes in blood pressure from baseline to the endpoint (at the end of four weeks);
- Changes in lipid prolife from baseline to the endpoint (at the end of four weeks);
- Improvement in quality of life score (EQ-5D questionnaire).

STATISTICAL ANALYSIS

Statistical analysis was performed with the help of statistical package SPSS (Statistical package analysis package for the social sciences) version 11.0.1. A p-value <0.05 was considered statistically significant.

Baseline characteristics of the study patients were tabulated by descriptive statistics (mean and standard deviation) and were compared with fourth week measurements after drug therapy using Paired sample t-test.

The analysis of primary parameters were done by using "One-way ANOVA" and "Bonferroni post-hoc test" at the baseline and at the end of first, second, third and fourth week of Losartan therapy.

The analysis of quality of life at the baseline and at the end of fourth week of losartan therapy was compared by using "Paired sample t-test" The quality of life scoring were done by using EQ-5D Health questionnaire using "Pearson chi-square test".

RESULTS

After screening, 50 hypertensive patients with dyslipidemia who full filled the eligible criteria and willing to participate were included in the study.

Majority of patients were aged between 50-60 years [Table/Fig-1]. There were no statistically significant changes in the baseline parameters after four weeks of losartan therapy except for random sugar which reduced significantly after losartan therapy(p=0.039) [Table/Fig-2].

The difference in SBP from baseline was significant at the end of first, second, third and fourth week after losartan therapy [Table/Fig-3]. The difference in DBP from baseline was significant at the end of first, second, third and fourth week after losartan therapy with p <0.0001 [Table/Fig-4]. Reduction in lipid profile values at the fourth week after losartan therapy when compared to baseline was significant [Table/Fig-5].

The parameters pain and anxiety/depression showed statistically significant improvement with p<0.044 and p<0.001 respectively [Table/Fig-6]. Twenty hypertensive patients had impaired quality of life at the baseline whereas the other 30 had normal quality of life. One patient had moderate impairment of mobility which did not improve after losartan therapy (p=1.000). Three patients had moderate impairment of self-care and two of them got improved after losartan therapy (p<0.159). Two patients had moderate impairment of usual activity which did not improve after losartan therapy (p=1.000). Four patients had moderate pain which got improved after losartan therapy (p<0.044). Ten patients had some anxiety/depression which got improved after losartan therapy (p<0.001). There was 100% improvement in pain and anxiety/depression parameters after Losartan therapy [Table/Fig-7].

Demographic characters	Number of patients (n=50)
Age in years:	
30-40	8
40-50	12
50-60	30
Sex:	
Male	27
Female	23

[Table/Fig-1]: Baseline demographic characteristics.

	Baseline		4th Week		p-value
	Mean	± S.D	Mean	± S.D	
SGOT(IU/L)	38.18	8.48	38.78	5.00	0.555
SGPT(IU/L)	33.10	5.76	33.10	5.34	1.000
Total Bilirubin(mg%)	0.74	0.13	0.74	0.13	1.000
ALP(IU/L)	70.06	17.09	73.22	18.46	0.071
Blood urea (mg/dL)	24.22	5.50	24.60	4.56	0.506
Random sugar (mg/dL)	117.78	28.51	113.00	23.21	0.039*
Serum Creatinine (mg/dL)	0.84	0.16	0.84	0.13	1.000
Serum Sodium (mEq/L)	138.80	4.27	137.92	3.37	0.162
Serum Potassium (mEq/L)	4.15	0.44	4.11	0.41	0.290

[Table/Fig-2]: Comparison of the data at baseline and at 4th week.
*p-value significant, paired sample t-test

Primary Efficacy Parameters

SBP	Mean	± S.D	95% Confidence Interval		p-value
			Lower Bound	Upper Bound	
Baseline	154.54	10.71	151.50	157.58	
First week	147.16	10.68	144.13	150.19	
Second Week	144.20	10.81	141.13	147.27	<0.0001*
Third Week	140.08	10.14	137.20	142.96	
Fourth Week	138.16	11.05	135.02	141.30	

[Table/Fig-3]: Changes in Systolic blood pressure.
*p<0.0001 was significant. One-way ANOVA and Bonferroni post-hoc test

			95% Confidence Interval		
DBP	Mean	± S.D	Lower Bound	Upper Bound	p-value
Baseline	91.56	7.17	89.52	93.60	
First week	87.92	7.70	85.73	90.11	
Second Week	86.12	7.75	83.92	88.32	<0.0001*
Third Week	83.68	7.06	81.67	85.69	
Fourth Week	82.44	7.89	80.20	84.68	

[Table/Fig-4]: Changes in diastolic blood pressure.
*p<0.0001 was significant. One-way ANOVA and Bonferroni post-hoc test

	Baseline		4th Week		
Lipid profile	Mean	± S.D	Mean	± S.D	p-value
Total cholesterol (mg/dL)	189.52	37.92	180.46	33.20	<0.0001*
LDL (mg/dL)	110.50	24.28	101.32	22.88	<0.0001*
Triglyceride (mg/dL)	135.68	21.87	127.70	19.24	<0.0001*

[Table/Fig-5]: Changes in lipid profile.
* p-value <0.05, statistically significant. One-way ANOVA and Bonferroni post-hoc test

	Baseline(n=50)		4th week(n=50)		
Quality of life	Mean	± S.D	Mean	± S.D	p-value
Mobility	1.02	0.14	1.02	0.14	-
Self Care	1.06	0.24	1.02	0.14	0.159
Usual Activity	1.04	0.20	1.04	0.20	-
Pain/Discomfort	1.08	0.27	1.00	0.00	0.044*
Anxiety/Depression	1.2	0.40	1.00	0.00	0.001*

[Table/Fig-6]: Changes in quality of Life score at the end of fourth week when compared to baseline.
*p-value<0.05 statistically significant. Paired sample t-test

No: of patients with moderate problem	Baseline (n=50)	After Losartan therapy (n=50)	p-value
Mobility	1	1	1.000
Self Care	3	1	0.159
Usual Activity	2	2	1.000
Pain/Discomfort	4	0	0.044*
Anxiety/Depression	10	0	0.001*

[Table/Fig-7]: Number of patients with impaired quality of life showing improvement after Losartan therapy.
*p<0.05 statistically significant. Pearson chi-square test

DISCUSSION

The present study was successful in demonstrating the pleiotropic effects of losartan in newly diagnosed hypertensive patients with dyslipidemia. Increasing systolic BP and diastolic BP will increase the risk of morbidity and mortality; for example high systolic pressure is associated with 2-3 fold increase in cardiac mortality. Hypertension with co-morbid conditions like abdominal obesity, insulin resistance, elevated catecholamines, elevated inflammatory markers like C - reactive protein and dyslipidemia with high plasma triglyceride, low high-density lipoprotein leads to adverse cardiovascular outcomes. Underlying mechanism may be due to expansion of plasma volume or over activity of sympathetic system [3].

Losartan act as a competitive antagonist of the thromboxane A2 receptor and therefore, can attenuate platelet aggregation. Its active metabolite EXP 3179 will reduce the COX-2 mRNA up regulation and so decreasing the prostaglandin generation. Losartan in the therapeutic dose of 50 mg daily significantly reduces serum total cholesterol and total triglyceride levels. Lipid lowering property of angiotensin receptor blocker is due to different mechanisms:

- Activation of PPAR gamma which regulates lipid metabolism;
- Interaction between the lipid metabolism and angiotensin system [9].

Mean age of the participants in this study was 51.48 years. Hypertension with dyslipidemia was more common in men when compared to women.A similar study done by Li-ying Chen found that incidence of dyslipidemia in middle aged males were higher than females [10].

These patients were at increased risk of cardiovascular disease which may be explained by increase in the C-reactive protein and endothelial dysfunction associated with these co-morbid conditions. Moreover, hyperinsulinemia and hypertriglyceridemia will lower renal uric acid excretion favouring the incidence of hyperuricaemia in hypertensive patients. Kretowicz M et al., explained that Losartan therapy decreased glycation end products and so improved insulin sensitivity and it also had a beneficial effect on endothelial dysfunction as assessed by decrease in vWF:Ag level [11].

Losartan is an already established effective once daily blood pressure lowering drug with excellent tolerability by blocking of angiotensin II at the type 1 receptor. In our study, the mean systolic blood pressure was reduced from 154.54 mm Hg to 138.16 mm Hg with p<0.0001 and the mean diastolic blood pressure was reduced from 91.56 mm Hg to 82.44 mm Hg with p<0.0001 after losartan therapy. Thus losartan was efficacious in decreasing the BP and it maintained the reduction. LIFE study done by Bjorn Dahlof et al., in 9193 patients showed a blood pressure fell by 30.2/16.6 mm Hg in losartan group when compared to 29.1/16.8 mm Hg in atenolol group. LIFE study showed that losartan prevented more cardiovascular morbidity and mortality than atenolol for a similar reduction in blood pressure and was well tolerated [12].

Dyslipidemia is associated with cardiovascular risk and so lipid management is necessary in hypertensive patients. Moreover, triglyceride synthesis is associated with increased uric acid production and there is a negative correlation between HDL-c and uric acid in hypertensive patients with dyslipidemia. There is

an implication that ARBs have beneficial effect on lipid profile. In our study, Losartan therapy significantly reduced the mean total cholesterol from 189.52 to 180.46 mg/dl, mean LDL from 110.50 to 101.32 mg/dl and mean triglygeride from 135.68 to 127.70 mg/dl with p<0.0001.A similar study done by Kyvelou SM et al., in 2438 patients with essential hypertension showed a significant reduction in total cholesterol(220 ±39 to 216±36mg/dl), LDL(from 146±35 to 141±33mg/dl), triglyceride levels(from 130±63 to 128±61mg/dl) and additionally HDL levels were increased from 48.2±12.2 to 48.8±11.9 mg/dl, p<0.0001 after Losartan therapy [9]. Thereby, losartan has a uniquely beneficial metabolic effect in addition to BP lowering.

There is a bidirectional and causal relationship between hyperuricaemia and hyperinsulinaemia (caused by insulin resistance) in hypertensive patients, the former favours free radical production by reducing nitric oxide bioavailability and the latter decreasing the renal excretion of urate. Losartan improves insulin sensitivity by reducing sympathetic activation and oxidative stress; and by increasing the tissue blood flow [11]. In our study, Losartan therapy significantly reduced the mean blood sugar from 117.78mg/dl to 113mg/dl with p<0.039.A similar study done by Marek Kretowicz et al in patients with mild to moderate essential hypertension showed a significant decrease in mean glucose level from baseline by 5.17mmol/l(p<0.05) after losartan therapy [11].

Several studies in the last 25 years have confirmed that hypertension has an impact on health related quality of life apart from the clinical and economical implications. It has been estimated that many patients with hypertension suffer from headache, dizziness, depression, anxiety and tiredness. Study conducted by Mamas Theodorou et al., and Wang et al., showed that anxiety and depression were the dimensions most frequently affected(27.6%) while self-care and usual activities were the least affected dimensions [13,14].

These study results highlights the fact that proper treatment of hypertension is necessary for the improvement of clinical index (i.e., decrease in BP), and for the patient's social and psychological well-being. In contrast to psychological well-being, hypertension did not show strong association with mobility and physical activities, indicating that physical activities were not limited to a large extent by hypertension [13,14].

We found that the reduced health-related quality of life in study patients with hypertension was to a greater extent a product of anxiety and depression than of physical health. Anxiety, depression and pain improved significantly with losartan therapy while usual activity, mobility and self-care did not improve significantly. Improvements in both anxiety and depression, as well as other dimensions, paralleled with improvement of the clinical picture.

LIMITATION

There were few limitations in our study. It was an open label, non-comparative study with small sample size and patients were followed up for short duration of one month only. There was significant reduction in random blood sugar level which might be because of change in the daily lifestyle of the patients. Secondly, the effect on life score mainly anxiety/depression might be because of change in mental status of the patients and not because of losartan. In future, multicentric study with large sample size and focus on uricosuric property of Losartan are recommended to generalize the results.

CONCLUSION

We conclude that, this study may have an implication of choosing an appropriate antihypertensive agent in hypertensive patients with dyslipidemia, a common co-morbidity of hypertension. Based on the results of our study, Losartan is safe and effective in treating hypertensive patients with dyslipidemia in addition to its antihypertensive effect and it also has benefits of reducing serum glucose, lipid levels and improvement in the quality of life.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Dermatology, Venereology and Leprology, Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamil Nadu, India.
2. Tutor, Department of Pharmacology, Tirunelveli Government Medical College, Tirunelveli, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sivakumar Sivasubramaniam,
9-B, Nachiyar Palayam Road, Woraiyur, Trichy-620003, Tamil Nadu, India.
E-mail: om.siva55@gmail.com

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