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Research Article

URICOSURIC EFFECTS OF LOSARTAN IN HYPERTENSIVE PATIENTS WITH HYPERURICAEMIA

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A B S T R A C T

Background: Epidemiological and experimental evidence suggest that serum uric acid is an important independent risk factor for cardiovascular and renal disease especially in patients with hypertension.In contrast to other angiotensin II antagonists, Losartan has unique pleiotropic uricosuric property and thereby reducing the risk of future cardiovascular complications in hypertensive patients.

Aim: To study the uricosuric effects of losartan in newly diagnosed hypertensive patients with hyperuricaemia.

Methodology: Open label, prospective and interventional study done after IEC approval. Newly diagnosed patients with stage 1 and stage 2 essential hypertension with hyperuricaemia who fulfilled the inclusion criteria were enrolled for the study and given Losartan. At the end of 4th week all the baseline laboratory parameters like renal function test, liver function test, and serum uric acid and urinary uric acid excretion were performed and results were analysed statistically

Results: After Losartan therapy mean serum uric acid was reduced from 6.43mg/dl to 5.33mg/dl and mean urinary uric acid excretion was increased from 418.12mg/day to 467.84mg/day which was significant.

INTRODUCTION

Hypertension is a worldwide epidemic defined as Blood pressure in excess of 140/90mmHg. Worldwide approximately 1 billion people have hypertension, contributing to more than 7.1million deaths per year[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, fetal 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 "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.

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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]. Epidemiological and experimental evidence suggest that serum uric acid is an important independent risk factor for cardiovascular and renal disease especially in patients with hypertension[6,7]. Raised serum uric acid level is found in approximately 25% of untreated hypertensive patients[8]. The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow and ischemia which will stimulate urate reabsorption and increase in uric acid synthesis respectively[8]. Hyperuricaemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheology and aggregation[6, 7]. Moreover; serum uric acid is positively correlated with blood pressure, body mass index, levels of fasting plasma glucose, triglycerides, high-sensitivity C - reactive protein and inversely correlated with HDL-c[7]. Losartan is an antihypertensive drug blocking the angiotensin II type1 receptors, it also has pleiotropic uricosuric effect by reducing postsecretory reabsorption of uric acid in the proximal tubule of the kidney by inhibiting urate/anion

exchanger and with placebo like side effect profile and this hypouricemic effect does not occur with other angiotensin receptor blockers[9,10]. According to JNC-8 guidelines, 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 55years old[11]. A number of pharmacological interventions like xanthine oxidase inhibitors (eg:allopurinol), sulfinpyrazone, benzbromarone and benziodarone can lower elevated serum uric acid levels but it is unknown whether these agents reversibly impact cardiovascular outcomes. However, LIFE (Losartan intervention for endpoint reduction in hypertension) study in patients with hypertension suggest the possibility of a treatment induced reduction in serum uric acid may indeed attenuate cardiovascular risk[6]. Serum uric acid should therefore be considered along with other risk factors such as obesity, hyperlipidemia and hyperglycemia, in the assessment of overall cardiovascular risk[6]. In contrast to other angiotensin II antagonists, Losartan has unique pleiotropic uricosuric property and thereby reducing the risk of future cardiovascular complications in hypertensive patients. Clinical studies have demonstrated that losartan is as effective as an ACE inhibitor, a calcium antagonist or a beta blocker in reducing the blood pressure but very few studies were done in India regarding its uricosuric effect. So the present study is done to focus on the uricosuric effect of losartan in newly diagnosed hypertensive patients with hyperuricaemia.

Aim of the study

To study the uricosuric effects of losartan in newly diagnosed hypertensive patients with hyperuricaemia.

METHODOLOGY

Study type: Interventional clinical study

Study design: Open label, prospective clinical study.

Study period: July 2016 to February 2017(8 months)

Study duration: January 2016 to August 2017(18 months)

Study sample : 54 hypertensive patients with hyperuricaemia.

Study drug and dosage: Losartan 50mg OD for 4weeks

Study place: Hypertention Out Patient Department, Tirunelveli medical college, Tirunelveli.

Ethical considerations

Approval from Institutional Ethical Committee of Tirunelveli Medical College Hospital was obtained, before starting the clinical study. Written informed consent was obtained in local vernacular language from every patient before enrollment.

Inclusion criteria

- 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>18years old and <60years old.
- Hyperuricaemia(>6mg/dl for women and >6.5mg/dl for men)

Exclusion criteria

- Secondary hypertension
- Hypertensive patients on antihypertensive drugs
- Patients with hepatic disease.
- History of gout and renal lithiasis within the last 2years
- Patients with myocardial infraction,angina and heart failure within the last 3 months
- Patients receiving any drugs that affect serum uric acid (eg: aspirin and allopurinol).
- Pregnancy and lactation
- Those with history of allergic reactions to study drugs.
- Age <18years old and >60years old
- History of neurologic or mental disorders

Withdrawal criteria

- Blood pressure >= 180/110 mmHg
- Protocol deviation
- Request for withdrawal by the subject
- Noncompliance with protocol
- Adverse effects(decision about withdrawal from the study was made either by investigator or subject)

Shedule of study visit

Screening and recruitment

Newly diagnosed patients with stage 1 and stage 2 essential hypertension with hyperuricaemia who fulfilled the inclusion criteria were enrolled for the study in the hypertension outpatient department. 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 10mins of calmness. Proper sized blood pressure cuff was used which covered at least 80% of the circumference of the upper arm. The cuff was wrapped around the upper arm with the cuff's lower edge one inch above the antecubital fossa and the stethoscope's bell was lightly pressed over the brachial artery just below the cuff's edge and the readings were noted by simultaneously observing the sphygmomanometer after rapidly inflating the cuff to 180mmHg and releasing air from cuff at a moderate rate (3mm/sec).
- Serum uric acid concentration and urine uric acid excretion were measured by enzymatic uricos method for all newly diagnosed hypertensive patients. For estimation of serum uric acid concentration 1ml of venous blood sample were withdrawn from patients under aseptic precautions. Patients were explained to collect every drop of urine during the day and night in an empty collection bottle and store the bottle at room temperature to get 24hours urine sample for estimation of urine uric acid excretion.Asper the inclusion criteria patients with hyperuricaemia (>6mg/dl in women and >6.5mg/dl in men) and essential hypertension were enrolled for the study.

- Liver function tests (SGOT, SGPT, Total Bilirubin and ALP) and renal function tests (serum creatinine bloodurea, serum potassium and sodium) were done in a random blood sample using automated analyser

Treatment protocol

The patients received T.Losartan 50mg once daily for a duration of four weeks. Patients were given 2weeks supply of drugs. Everyday morning T.Losartan was taken orally by all patients. 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 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, and serum uric acid and urinary uric acid excretion were performed.

Efficacy Parameters

Primary Endpoint

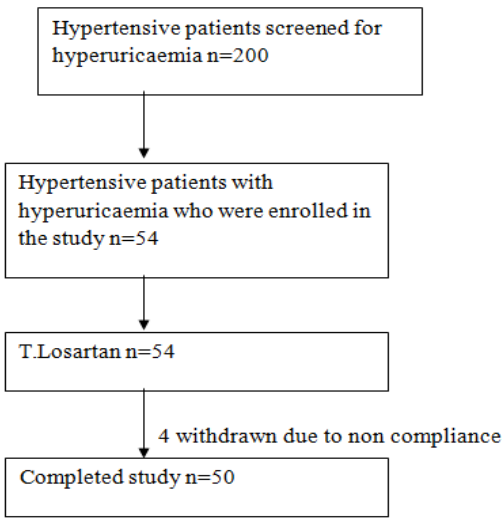
- Changes in serum uric acid from baseline to the endpoint(at the end of four weeks)
- Changes in urinary uric acid excretion from baseline to the endpoint(at the end of four weeks)

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

- Baseline characteristics of the study patients were tabulated by descriptive statistics (mean and standard deviation) and were matched with fourth week measurements after drug therapy using paired sample t test.
- The analysis of primary parameters was done by using "Student paired t test" at the baseline and at 4 weeks before and after giving Losartan.

Patient disposition



RESULTS

Over a period of 8 months from July 2015 to February 2016, totally 200 new cases diagnosed with hypertension in the outpatient department was screened for hyperuricaemia. After screening, 54 hypertensive patients with hyperuricaemia who full filled the eligible criteria and were willing to participate were included in the study. All the study participants were given T.Losartan 50mg once daily for four weeks. Four patients were withdrawn due to non compliance and totally 50 patients completed the study. The results were statistically analysed.

DISCUSSION

In essential hypertension, the comorbidity of hyperuricaemia is very common. In addition to hypertension, hyperuricaemia is linked to cardiovascular disease, stroke and decline in renal function. So there is a therapeutic advisability of serum urate reduction in the management of hypertension. In hypertensive patients with hyperuricaemia, conventional uric acid lowering agents like allopurinol, probenecid or febuxostat significantly reduced serum urate but failed to reduce blood pressure significantly and did not reverse the cardiovascular risk. Moreover these agents were poorly tolerated[12].

In this regard, in recent years Losartan, an angiotensin receptor blocker is of potential interest. Previous studies have shown that losartan reduces serum uric acid and importantly, this hypouricaemic effect does not occur with other angiotensin receptor blockers. The uricosuric effect of Losartan does not appear to be mediated by angiotensin inhibition. Hypouricaemic effect of Losartan is mediated through reduction in the level of human urate transporter 1 and so decreased net urate reabsorption in the proximal tubule of kidney[13]. In addition Losartan significantly increases urinary pH, an interesting property, not shared by other uricosuric drugs, which counter balances the risk of uric acid stone associated with increased uric acid excretion. Our study was successful in evaluating the uricosuric effect of Losartan in hypertensive patients with hyperuricaemia. Mean age of the participants in this study was 51.48years. Hypertension with hyperuricaemia was more common in men when compared to women. This may be due to estrogen in women promoting uric acid excretion. A similar study done by Li-ying Chen found that incidence of hyperuricaemia in middle aged males were higher than females[14]. Fourteen patients in our study suffered from co-morbid conditions like hypercholestremia, type 2 diabetes mellitus and hypothyroidism.

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. Marek *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[15] Several epidemiological studies have shown that increased serum uric acid might be an independent risk factor for hypertension-associated morbidity and mortality. Moreover hyperuricaemia is associated with increased risk of

cardiovascular death by 12%. In adolescents, serum uric acid >5.5mg/dl was observed in 89% of newly diagnosed patients with essential hypertension[16]. So lowering serum uric acid in hypertensive patients may prevent the morbidity and mortality. In our study, losartan showed significant reduction in mean serum uric acid from 6.43mg/dl (baseline) to 5.33mg/dl (fourth week) with p<0.0001. The mean urinary uric acid excretion was increased from 418.12mg/day (baseline) to 467.84md/day (fourth week) with p<0.001. After four weeks of therapy, the percentage decrease in serum uric acid was 17.11% and increase in urinary uric acid excretion was 11.89%. This was statistically significant.Similar studies done by SimaAbediAzar *et al.*,[17] Moosa Khan *et al.*[18] and Gianni Mingheli *et al.*[19], showed that losartan therapy had significant effect in reducing hyperuricaemia and increasing urinary excretion of uric acid by lowering tubular reabsorption of uric acid. Therefore Losartan may be a good option in hypertensive patients with hyperuricaemia and also in preventing hypertension associated morbidity and mortality.

Limitations

There were few limitations in our study. It was an open label, non comparative study with small sample size

CONCLUSION

We conclude that, this study may have an implication of choosing an appropriate antihypertensive agent in hypertensive patients with hyperuricaemia, a common co-morbidity of hypertension. Based on the results of our study, Losartan is safe and effective in treating hypertensive patients with hyperuricaemia due to its uricosuric effect in addition to its antihypertensive effect

Acknowledgement

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No funding

Table 1 Baseline demographic charecteristics

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

- Majority of patients were aged between 50-60 years
- Hyperuricaemia was more common in men(n=27) when comparedto females(n=23)

Table 2 baseline investigations

	Baseline		4th Week		
	Mean	± S.D	Mean	± S.D	P value
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	24.22	5.50	24.60	4.56	0.506
Random sugar	117.78	28.51	113.00	23.21	0.039
Serum Creatinine	0.84	0.16	0.84	0.13	1.000
Serum Sodium	138.80	4.27	137.92	3.37	0.162
Serum Potassium	4.15	0.44	4.11	0.41	0.290

Table 2 There were no statistical significant changes in the baseline parameters after four weeks of losartan therapy except for random sugar which was reduced significantly after losartan therapy(p=0.039)

Primary Efficacy Parameters

Table 3 Changes in serum uric acid and urinary uric acid at the end of fourth week after Losartan therapy compared with baseline

	Baseline		4th Week		
	Mean	± S.D	Mean	± S.D	P value
Serum uric acid	6.43	0.29	5.33	0.86	<0.0001
Urinary uric acid	418.12	102.19	467.84	88.52	<0.0001

* p value <0.05, statistically significant

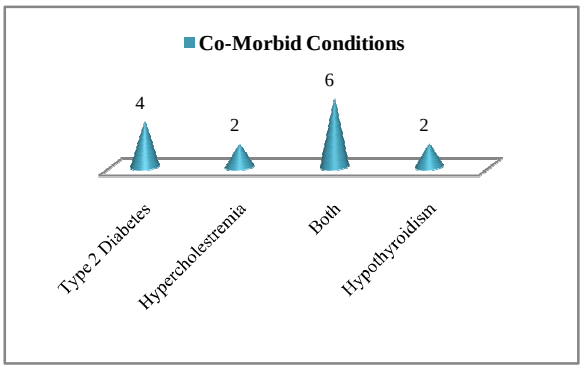

Figure 1 Co-Morbid Conditions

- 14 study participants suffered from associated diseases like type 2 diabetes mellitus, hypercholestremia and hypothyroidism.
- ➢ 4 (7.4%)patients had type 2 diabetes mellitus
- ➢ 2 (3.7%)patients had hypercholestremia
- ➢ 6(11.1%) patients had both diabetes and hypercholestremia
- ➢ 2 (3.7%)patients had hypothyroidism

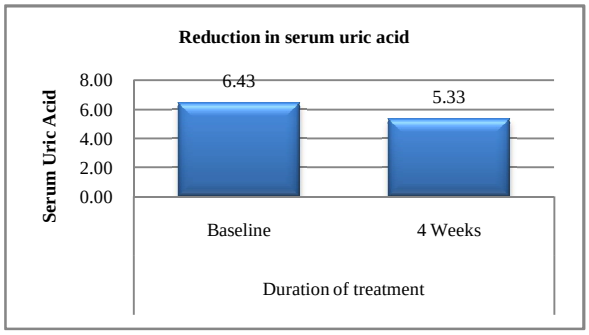

Figure 2 Pictorial representation of reduction in serum uric acid after 4 weeks of Losartan therapy

- ➢ After Losartan therapy mean serum uric acid was reduced from 6.43mg/dl to 5.33mg/dl

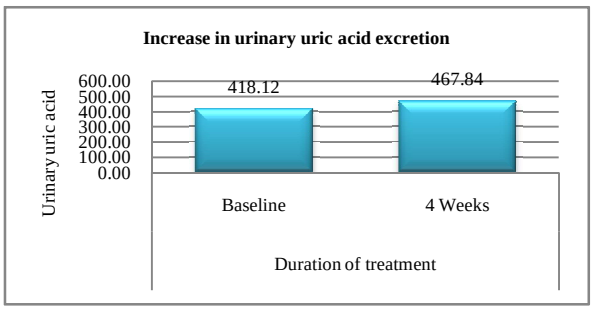

Figure 3 Pictorial representation of increase in uric acid excretion

- Mean urinary uric acid excretion was increased from 418.12mg/day to 467.84mg/day after Losartan therapy

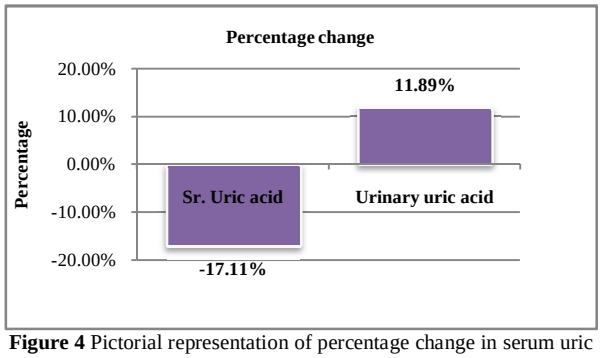

Figure 4 Pictorial representation of percentage change in serum uric acid and urinary uric acid after Losartan therapy

- 17.11% reduction in serum uric acid and 11.89% increase in urinary uric acid excretion was achieved after four weeks of Losartan therapy

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