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**Original Article**

# The effects of Amlodipine plus Losartan combination versus Amlodipine alone on serum uric acid levels in hypertension at a tertiary care hospital of north India

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***ABSTRACT***

The present study is designed to evaluate the effects of Amlodipine (AMLO) versus Amlodipine plus Losartan (LOS) on serum uric acid (SUA) levels and on other biochemical parameters in hypertension. 60 newly diagnosed hypertensive patients were assigned into two groups randomly. First group (30 patients) were treated with Amlodipine (5mg to 10mg) and Losartan (25mg to 50mg) combination once daily and the second group (30 patients) were treated with Amlodipine (5mg to 10 mg) alone once daily. SUA levels were recorded before the start of treatment, after 6 weeks and after 12 weeks. Statistical analysis was done using paired t test. Out of 30 patients in each group, it was observed that the mean SUA reduction with the combination of AMLO and LOS (14.13%) was more as compared to AMLO alone (10.15%) and this difference is statistically significant ($p<0.05$). The serum levels of sodium, potassium and urea were same whereas the serum levels of creatinine were decreased from baseline to 12 weeks (3.93% decrease).The serum cholesterol was decreased by 2.43% from baseline to 12 weeks. Both treatments were efficacious in reducing serum uric acid levels but the combination therapy showed greater reduction than monotherapy.

**Key words**: Hypertension, Amlodipine, Losartan, Serum uric acid.

## INTRODUCTION

Hypertension is described as systemic blood pressure of 140/90mmHg or more on two separate occasions measured at least one to two weeks apart.[1]There are various studies which have shown that there is strong association between HTN and coronary artery diseases, myocardial infarction, congestive heart failure, stroke and vascular disease and thus lowering the blood pressure (BP) will significantly reduces all these morbidities.[2] HTN being recognized as a major risk factor to many vascular diseases and the need for therapy was soon realized by many pharmaceutical industries. So, the discovery of effective and safe medications to control BP was a potential gold mine.[3]Calcium channel blockers e.g Amlodipine, Felodipine, Nifedipine, Verapamil, Diltiazem which inhibit influx of calcium through voltage sensitive calcium channels as calcium triggers contraction in cardiac myocytes and in smooth muscles. Angiotensin receptor antagonist precisely AT1 receptor antagonist antagonize the effects of angiotensin II thereby promote vasodilatation, increase renal salt and water excretion.[4] Antihypertensives agents are given to many patients having hyperuricemia because both the conditions can exist together and how they decrease the levels of SUA depends on their mechanism of action. Calcium channel blockers decreases the serum uric acid levels whereas the angiotensin receptor blockers (ARBs) decreases or increases the SUA levels, it depends on the type of drug like losartan decreases the SUA levels as it block the urate transporter 1(URAT 1) in the proximal tubule whereas valsartan and candesartan increases the SUA levels in patients with hypertension. [5] Addition of calcium channel blockers to ARBs is reported to increase the antihypertensive efficacy of ARBs. But concurrently in view of reported increase of SUA levels by certain ARBs except losartan, question arises whether this increased antihypertensive efficacy of combination leads to decrease in SUA levels because both the drugs decrease SUA level to some extent. Therefore, we are decreasing high blood pressure and at the same time decreasing SUA levels but is this combination decreases more SUA levels as compared to the calcium channel blocker if given alone is questionable. The present study is designed to evaluate the effect of fixed

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dose combination of AMLO (5 mg to 10mg) plus LOS (25mg to 50mg) versus fixed dose of AMLO (5mg to 10 mg) on SUA levels and on other biochemical parameters.

## MATERIAL AND METHODS

It is prospective, randomized, open parallel group comparative study. The study protocol was approved before the commencement of the study by the institutional ethics committee. The patients of either sex between the age of 18 years and 70 years attending outpatient department of medicine were screened and 75 patients were registered for the study after fulfilling the inclusion and exclusion criteria and giving the written informed consent. Out of 75 patients, 15 patients were declared drop. Thus only 60 patients were enrolled in the study. Patients were assigned either of two groups (group I and group II) randomly. First group (group I) will comprise 30 patients that will be treated with AMLO 5 mg to 10 mg plus LOS 25 mg to 50 mg once daily and the second group(group II) will have another 30 patients that will be treated with AMLO 5 mg to 10 mg once daily. Patients with secondary hypertension, patients with impaired liver and/or kidney function, pregnant and lactating females and those taking oral contraceptives were excluded from the study. Diagnosis was made on the basis of JNC -8 criteria. Study subjects were evaluated for a period of 12 weeks. The study was conducted by pharmacology department in collaboration with medicine department, MMIMSR, Mullana, Ambala.

The SUA levels were measured before giving treatment in both the groups, at 6 weeks and at 12 weeks of treatment whereas the serum sodium, serum potassium, serum urea, serum creatinine and serum cholesterol was measured before and at 12 weeks of treatment. SPSS 21.0 V Statistical Software and Excel Microsoft were used to analysze and present the data collected in this research study.

## OBSERVATION AND RESULTS

The mean SUA $\pm$SD in group I at baseline, 6 week and at 12 week was 5.77$\pm$1.28, 5.28$\pm$1.13, 5.14$\pm$1.05mg/dl respectively whereas the mean SUA $\pm$SD in group II at baseline, 6 week, 12 week was 5.19$\pm$1.15, 4.87$\pm$0.97 and 4.82$\pm$1.05 mg/dl respectively. The difference in the SUA levels in the two groups at 6 week was insignificant ($p>0.05$) but at 12 week it was significant ($p<0.05$). The change in the SUA levels from baseline to 12 weeks was more in group I as compare to group II and this difference is significant(<0.05) as shown in table 1,figure 1 and figure 2.

Table 2 depicts the effects of AMLO plus LOS combination and AMLO alone on other biochemical parameters. In group I there was significant decrease in the mean value of serum cholesterol ($p<0.001$) whereas no significant changes are found in the mean serum levels of urea, creatinine, sodium and potassium.

In group II there was significant increase in the mean value of serum creatinine ($p<0.001$) and significant decrease in the mean value of serum cholesterol ($p=0.005$) whereas no significant changes are found in the mean serum level of urea, sodium and potassium.

## *DISCUSSION*

Affecting 1 billion population worldover, hypertension remains one of the leading causes of death worldwide making it a public health problem. Moreover, hypertension is also associated with various comorbid conditions and one of them is gout. It is also a leading cause for hospitalization and outpatients visits. Despite a large number of antihypertensives which are in current clinical use, in the present study, the two commonly used groups of agents were considered for comparative evaluation on serum uric acid levels as both the condition can co-exist. Since, antihypertensive therapy has to be continued almost throughout the life of an individual, therefore effect on laboratory parameters between two regimens are quite important, while comparing the two regimens.

In the present study, majority of patients belonged to the age group of 51 to 60 years and the number of males and female were almost equal and this observation are in agreement with the Gupta R[6] from Jaipur who demonstrated rising prevalence of hypertension by 30%, 36% and 51% among males and 34%, 38%, and 51% among females through three serial epidemiological studies carried out during 1994, 2001 and in 2003 respectively.

In group I subjects the mean SUA levels were decreased by 10.92% from baseline to 12 week whereas in group II subjects the mean serum uric acid levels were decreased by 7.13% ($p<0.05$) and this finding correlates with the findings of study by Shusuke Yagi et al [7] in which angiotensin II receptor blocker (ARB) and calcium channel blocker (CCB) combination was given to determine its effect on blood parameters. The combination contains tablet of regular dose of irbesartan (100 mg) and a high dose of amlodipine (10 mg) were given on 68 patients for 3 months. The mean levels of serum uric acid before treatment was 5.5$\pm$ 1.5 mg/dl and after 3 months it was significantly

reduced to 5.1±1.3 mg/dl (p<0.001) which was less as compare to the present study. In our study the difference from baseline to 12 week was 0.63mg/dl in combination group whereas in another study done by Pratibha Salve S et al [8] to see the effects of calcium channel blockers (CCBs) especially Amlodipine on different biochemical parameters in hypertensive patients. In their study, 39 patients with mild to moderate hypertension were prescribed mono drug therapy with amlodipine for six months. At the end of six month it was found that there was significant decrease in total cholesterol (TC), SUA level and significant increase in HDL cholesterol. The mean serum uric acid levels were 4.33±0.93 mg/dl before the start of the study and were 3.92 ± 0.68 mg/dl at the end of six months. The difference from baseline to 6 month was 0.41mg/dl(p<0.003) which was more as compared to the present study as in our study the reduction in serum uric acid from baseline to 12 weeks was 0.37mg/dl.

In patients of group I the serum urea had decreased from baseline to 12 weeks but this decrease was not statistically significant (p>0.05), the serum creatinine had increased from baseline to 12 weeks but this increase was not statistically significant and this observation correlates with Shusuke Yagi et al[7] where the mean levels of serum creatinine with ARB+CCB group at the baseline period was 0.82±0.24 mg/dl and rises insignificantly to 0.81±0.24 after 3 months and the mean levels of serum urea before and after 3 months of treatment rises insignificantly (p<0.05).

The serum levels of sodium and potassium levels decreases from baseline to 12 weeks but this decrease was statistically insignificant and these findings are in agreement with study by Shusuke Yagi et al [7] where similar results were found with amlodipine and irbesartan combination therapy.
Regarding effect on serum cholesterol, it decreases significantly statistically (p<0.001) and this finding correlates with the study by Kohlmann O Jr et al[9].

In patients of group II the serum urea decreases from baseline and this decrease was not statistically significant whereas the serum levels of creatinine increases from baseline to 12 weeks and this findings was statistically significant(p<0.001) and this findings correlates with the results by Iram Shaifali et al [10] with amlodipine drug and found that mean serum creatinine at baseline and after 24 weeks was 0.674±0.01 to 0.732±0.01 mg/dl (p<0.05) and mean serum urea at baseline and at 24 weeks rises insignificantly (p>0.05).

The serum levels of sodium and potassium decreases from baseline and this is statistically insignificant and this finding correlates with the finding by Pratibha Salve S et al [8] with amlodipine drug. Regarding effect on serum cholesterol, a statistical significant reduction (p=0.005) was observed from baseline to 12 weeks and this finding is in line with the findings by Pratibha Salve S et al [8] with amlodipine drug where the mean levels of serum cholesterol before treatment was 197.85 ± 29.50 mg/dl which decreases (p<0.014) significantly to 190.49 ±25.74 after 6 months of drug therapy.

## *CONCLUSION*

In conclusion, comparatively speaking, both amlodipine plus losartan combination and amlodipine alone decreases the serum uric acid levels but the combination therapy showed greater reduction in lowering serum uric acid levels over the monotherpay. Further in cases of hypertension associated with hyperuricemia due to any cause the choice of antihypertensives are very crucial so that both the conditions can be treated together or as a prophylaxis for the patients who are at risk of hyperuricemia. But in cases of hypertension associated with gout, the specific antigout drugs are required along with such antihypertensive drugs.

**TABLE 1**

| Time interval | Group I | | Group II | | p value (Gp I vs. Gp II) |
|---|---|---|---|---|---|
| | Mean±SD | p value | Mean±SD | p value | |
| Baseline | 5.77±1.28 | ref | 5.19±1.15 | ref | 0.069 |
| 6 week | 5.28±1.13 | <0.001 | 4.87±0.97 | <0.001 | 0.140 |
| 12 week | 5.14±1.05 | <0.001 | 4.82±1.05 | <0.001 | 0.010 |

**Figure 1:Serum uric acid levels of group I at baseline, 6 weeks and at 12 weeks**

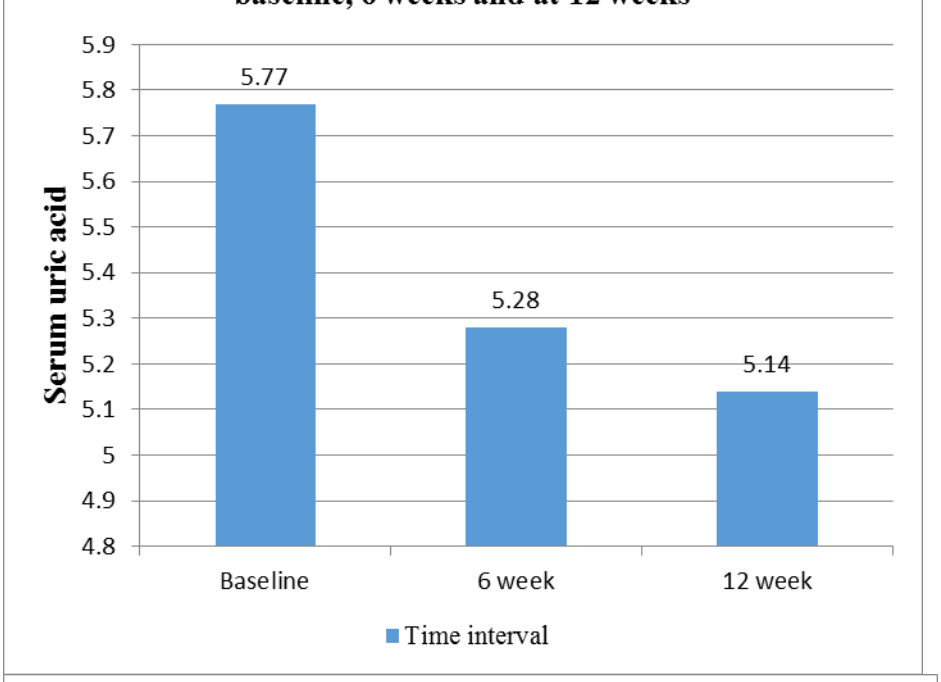


**Figure 2:Serum uric acid levels of group II at baseline, 6 weeks and at 12 weeks.**

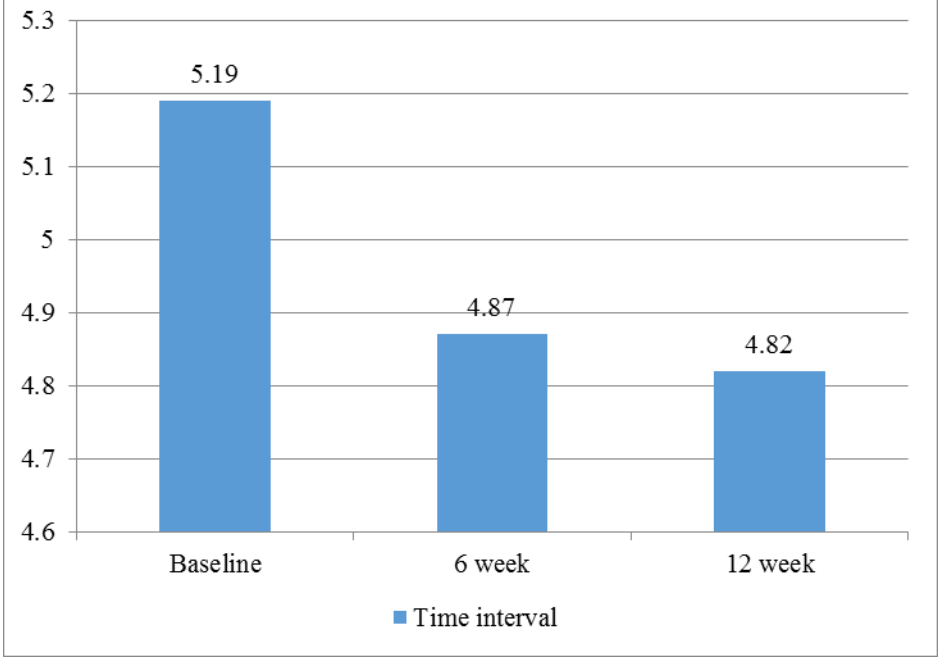

TABLE 2

| Time interval | Group I(AMLO plus LOS) | Group II(AMLO) | p value |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Baseline(UREA) | 29.50±5.04 | 29.43±5.34 | 0.961 |
| After 12 weeks(UREA) | 28.76±4.93 | 29.27±5.61 | 0.715 |
| p value (baseline vs. 12 weeks) | 0.044 | 0.654 | - |
| Baseline(CREATININE) | 0.90±0.20 | 0.87±0.24 | 0.649 |
| After 12 weeks(CREATINNE) | 0.91±0.18 | 1.44±0.36 | <0.001 |
| p value (baseline vs. 12 weeks) | 0.517 | <0.001 | - |
| Baseline(SODIUM) | 139.70±4.23 | 138.87±3.81 | 0.426 |
| After 12 weeks(SODIUM) | 139.0±3.27 | 138.50±3.27 | 0.583 |
| p value (baseline vs. 12 weeks) | 0.059 | 0.281 | - |
| Baseline(POTASSIUM) | 4.55±0.57 | 4.52±0.51 | 0.058 |
| After 12 weeks(POTASSIUM) | 4.52±0.60 | 4.37±0.55 | 0.307 |
| p value (baseline vs. 12 weeks) | 0.843 | 0.278 | - |
| Baseline(CHOLESTEROL) | 162.03±17.15 | 155.80±23.43 | 0.245 |
| After 12 weeks(CHOLESTEROL) | 154.96±15.55 | 152.90±22.00 | 0.676 |
| p value (baseline vs. 12 weeks) | <0.001 | 0.005 | - |

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