# AN OBSERVATIVE STUDY OF COMPARISON OF EFFICACY AND TOLERABILITY BETWEEN LOSARTAN AND COMBINATION OF LOSARTAN AND AMLODIPINE IN THE MAINTENANCE THERAPY OF HYPERTENSION IN OPD OF GENERAL MEDICINE DEPARTMENT AT GIMS, KALABURAGI

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**ABSTRACT**

**BACKGROUND**

Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with advancing age. The beta receptor antagonists provide effective therapy for all grades of hypertension. Compared with other classes of antihypertensive agents, there is a greater frequency of achieving blood pressure control with Ca2+ channel blockers as monotherapy. Because of paucity of published reports in the literature regarding the pattern of use, efficacy, safety, tolerability of comparison of Losartan and Amlodipine and their combination was taken up in the present study.

Aims and Objectives- To study the comparison of efficacy, safety and tolerability of the combination of amlodipine and losartan and their combination in achieving blood pressure control.

**MATERIALS AND METHODS**

120 properly selected subjects with hypertension were included for the present study. The medication was used empirically as monotherapy or combination, OD in a regular manner. Blood pressure was measured at the baseline and daily afterwards for one month. The data collected was analysed statistically using descriptive statistics. Tolerability and patient compliance for the prescribed medications were also assessed during the follow up visits.

**RESULTS**

Blood pressure is maintained at the baseline level in all the study subjects. The two drugs were found to be equi-effective in reducing the blood pressure to the target goal, at their respective equivalent doses. Combination therapy found to have better efficacy and fewer side effects. The patient compliance for the prescribed medications was excellent.

**CONCLUSION**

Hypertension can be more effectively treated by combination therapy than monotherapy of Amlodipine.

**KEYWORDS**

Losartan, Amlodipine, Hypertension, Efficacy.

**HOW TO CITE THIS ARTICLE:** Kumar S, Bagewadi HG, Banderao PV. An observative study of comparison of efficacy and tolerability between losartan and combination of losartan and amlodipine in the maintenance therapy of hypertension in OPD of general medicine department at GIMS, Kalaburagi. J. Evid. Based Med. Healthc. 2018; 5(17), 1447-1451. DOI: 10.18410/jebmh/2018/303

## BACKGROUND

Hypertension (HTN), is an increasingly prevalent chronic condition and is associated as a reversible risk factor for myocardial infarction, heart failure, stroke, kidney disease and blindness.[1] Hypertension or high blood pressure is defined as systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mmHg, by the World Health Organization. At the turn of the millennium the global data revealed that 972 million adults or 26.4% of the adult population had HTN.[2] Persistently elevated blood pressure is estimated to be the underlying cause for about 54% of stroke, 47% of ischemic heart disease, and 25% of other cardiovascular diseases worldwide.[3]

There are many classes of antihypertensive drugs in the pharmaceutical armamentarium with different mechanisms of action. Among the most important and most widely used are the calcium channel blockers (CCBs), beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs) and the thiazide diuretics. ARBs are a newer and safer class of antihypertensive agents because of their superior efficacy and good tolerance.[4] Data from various Clinical trials like ELITE, VALIANT, LIFE, etc. have approved ARBs for diabetic nephropathy, stroke prophylaxis, heart failure and to reduce cardiovascular mortality in clinically stable patients with left ventricular dysfunction following myocardial infarction.[5] CCBs is another frequently

*Financial or Other, Competing Interest: None.*
*Submission 07-04-2018, Peer Review 12-04-2018,*
*Acceptance 20-04-2018, Published 23-02-2018.*
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*DOI: 10.18410/jebmh/2018/303*

prescribed antihypertensive. Amlodipine make up more than 85% of all CCBs prescribed.[6] Clinical trials like HOT, STOP- and ALLHAT have also found CCBs equi-effective as diuretics/β blockers/ACE inhibitors in reducing cardiovascular Mortality and in reducing the risk of fatal stroke by 44% to 55%. CCBs are especially suitable for the treatment of senior hypertensive patients and can be safely given in patients of asthma and PVD.[7] There have been several studies which have concluded that Losartan 50 mg has equal anti-hypertensive efficacy as 5mg of Amlodipine Monotherapy.[8-10] The selection of a first-line antihypertensive agent must be based not only on efficacy and outcome, but also tolerability and compliance, which includes both quality-of-life considerations and cost.[11] Amlodipine – a calcium channel antagonist dihydropyridine derivative, is a potent antihypertensive drug thanks to its potent action as an arterial vasodilator; it also has natriuretic, antiproliferative, and antisclerotic effects.[12,13]

However, calcium channel blocker antihypertensive drug class does not promote a venodilation comparable to the arterial effect; it creates an imbalance of hydrostatic forces in peripheral capillaries, and facilitates fluid extravasation into the interstitial space, which enables the formation of lower extremity oedema due to the gravity force.[12-14] Lower extremity oedema has been described as a frequent adverse effect of this antihypertensive drug class, and is frequently regarded as the cause of treatment dropout. The use of lower doses of this calcium antagonist is a way to minimize this effect, since there is a relation between dose used and frequency and intensity of adverse events.[17] However, clinical practice shows that a 50% reduction in the dose of this antihypertensive drug results in the loss of at least 20% of the hypotensive effect provided by the full dose, thus making the goal of controlling blood pressure difficult to achieve.[14]

An alternative to reduce or even to prevent calcium channel antagonist-induced lower extremity oedema is to combine a drug that also promotes venodilation. Similarly, to ACE (angiotensin converting enzyme) inhibitors, angiotensin II AT1 receptor blockers such as losartan promote both arterial and venous vasodilation, balancing hydrostatic pressure in peripheral capillaries, and thus reducing fluid extravasation into the interstitium.[15]

Therefore, in addition to potentiating the reduction in blood pressure, the use of the combination of these two antihypertensive drugs may provide a lower incidence of lower extremity oedema resulting from the use of a lower dose of amlodipine and from the venodilator effect of losartan.[16]

In this light, the present study was done to assess efficacy and tolerability between Losartan and combination of Losartan and Amlodipine in the maintenance therapy of hypertension.

## MATERIALS AND METHODS

This was a prospective, randomized, observational open label comparative clinical study of three months duration (Dec 2017- Feb 2018) which was conducted in OPD of department of General medicine at Gulbarga Institute of Medical Sciences, Kalaburagi. Patients of age 18-65 years, of both sexes, attending Medicine OPD were examined. Drug naive newly diagnosed patients of hypertension (conforming to Stage 1 JNC VIII) were enrolled. Written informed consent from all the participants/relatives was undertaken before the commencement of the study. The study protocol was approved by Institutional Ethical Committee. Patients of secondary hypertension, patients having significant cardiac disease, patients with impaired liver and/or kidney function, pregnant and lactating females and females taking oral contraceptive pill were excluded from the study. Thus, a total of 120 eligible patients who fulfilled the inclusion criteria were enrolled in the study. The study involved the use of a structured pretested and predesigned questionnaire to collect the demographic information and to measure subject's blood pressure. BP was recorded with standardized protocol using mercury column type sphygmomanometer and stethoscope. All BP values were expressed as the average of three measurements obtained at an interval of 15 minutes each. A total of 120 patients were then randomly divided into two groups. They were then randomized into three groups. Group 1 received treatment with Losartan (50 mg) i.e. LST Group (n=40). Group 2 received treatment with Amlodipine (5 mg OD) i.e. AMLO Group (n=40). Group 3 received treatment with combination of Amlodipine (5 mg OD) along with Losartan (50 mg OD).

The selection of doses of these two agents was based on previous studies which showed that Losartan 50 mg once daily and Amlodipine 5 mg once daily caused almost equal reduction of BP in patients of stage 1 Hypertension. Hence the two doses are considered equi-effective. Relevant Laboratory tests were carried out before the initiation of therapy and after twelve weeks of completion of treatment. Patients under treatment were subsequently monitored and re-assessed at regular follow-ups every week for evaluation of BP reduction or control and monitoring of adverse effects. Throughout the study period BP <140/90 mm Hg was targeted.

## RESULTS

A total number of 120 patients were enrolled in the study. None of the patients were lost during the follow-up period. Majority of the patients were in the age group of 40-50 years, although the incidence of Hypertension seems to be increasing from the age of 31 years onwards.

As shown in Table 1, Out of the 120 newly diagnosed cases of hypertension, males showed a higher prevalence (60%) of hypertension as compared to females (40%) and a greater number of patients belonged to urban areas (66) as compared to rural areas (33).

| Sl. No. | Items | LST | AMLO | LST+AMLO | Total |
|---|---|---|---|---|---|
| 1. | No. of Patients | 40 | 40 | 40 | 120 |
| 2. | Male | 24 | 24 | 24 | 72 (60%) |
| 3. | Female | 16 | 16 | 16 | 48 (40%) |
| 4. | Rural | 13 | 13 | 14 | 40 (33%) |
| 5. | Urban | 26 | 26 | 28 | 80 (66%) |
| 6. | Age, (years) | 46.7 ± 9.8 | 45.3 ± 8.4 | 48.8 ± 7.3 | |
| 7. | SBP, (mmHg) | 160.86 ± 6.36 | 162.64 ± 6.2 | 164.64 ± 4.72 | |
| 8. | DBP, (mmHg) | 96.17 ± 4.8 | 98.45 ± 4.2 | 100.45 ± 4.8 | |
| 9. | Mean, BM (Kg/m²) | 21.24 ± 2.7 | 20.84 ± 3.6 | 22.84 ± 2.4 | |

***Table 1. Baseline Characteristics of Randomized Patients***

Values expressed as Mean ± SD.

Table 2 shows the comparative evaluation of changes in mean SBP between the three groups. It was observed that although in all the three regimens, individually produced statistically significant reductions in SBP ($p < 0.05$) at 2nd and 3rd follow ups when compare to baseline values. But there was no statistically significant difference when the mean values of SBP, of LST and AMLO treated groups, were compared at each follow-ups. There was statistically significant reduction ($p > 0.05$) in mean values of SBP in LST +AMLO treated group when compared to AMLO treated groups, at each follow-up. There was also statistically significant reduction ($p > 0.05$) in mean values of SBP in LST +AMLO treated group when compared to LST treated group, at 1st follow-up.

| Items | SBP of LST Group | SBP of AMLO Group | SBP of (LST+AMLO) Group |
|---|---|---|---|
| Baseline | 160.75 ± 5.82 | 162.67 ± 5.12 | 164.34 ± 5.12 |
| 1st follow- up | 157.58 ± 3.74 | 158.33 ± 4.16 | 142.43 ± 4.16*, † |
| 2nd follow- up | 142.51 ± 3.51 | 138.78 ± 5.422 | 132.38 ± 5.32† |
| 3rd follow- up | 28.62 ± 3.75 ‡ | 130.54 ± 5.21 ‡ | 120.54 ± 5.21 ‡, † |

***Table 2. Comparative Evaluation of SBP with Three Regimens.***

Values expressed as Mean ± SD. *$p < 0.05$ versus LST, †$p < 0.05$ versus AMLO, ‡$p < 0.05$ versus (base line SBP of that group)

Table 3 shows the comparative evaluation of changes in mean DBP between the three groups. It was observed that although in all the three regimens, individually produced statistically significant reductions in SBP ($p < 0.05$) at 2nd and 3rd follow ups when compare to baseline values. But there was no statistically significant difference when the mean values of SBP of LST and AMLO treated groups, were compared at each follow-ups. There was statistically significant reduction ($p > 0.05$) in mean values of DBP in LST +AMLO treated group when compared to AMLO treated groups, at 3rd follow-up.

| Items | DBP of LST Group | DBP of AMLO Group | DBP of (LST+AMLO) Group |
|---|---|---|---|
| Baseline | 98.37 ± 4.2 | 100.45 ± 3.6 | 100.25 ± 3.6 |
| 1st follow- up | 94.54 ± 3.62 | 92.28 ± 2.32 | 90.38 ± 2.42 |
| 2nd follow- up | 90.38 ± 2.52 | 90.68 ± 2.64 | 86.38 ± 2.32 |
| 3rd follow- up | 88.18 ± 2.32‡ | 90.12 ± 3.22‡ | 80.48 ± 2.22,†,‡ |

***Table 3. Comparative Evaluation of DBP With Three Regimens***

Values expressed as Mean ± SD.*$p < 0.05$ versus LST, †$p < 0.05$ versus AMLO.

Table 4 depicts the comparative changes in Mean BP (MBP) in all the groups at baseline and at the end of the treatment. The result comes out to be statistically significant ($p < 0.05$), both Losartan and Amlodipine in given doses are equi-effective in reducing the BP when compared to baseline and at the end of the treatment.

| MBP of different groups | Baseline | Final visit | Mean Difference ± SD |
|---|---|---|---|
| LST | 118.73 ± 3.84 | 101.94 ± 4.16‡ | 17.79 ± 0.32 |
| AMLO | 119.84 ± 3.96 | 103.12 ± 4.42‡ | 16.72 ± 0.46 |
| LST+ AMLO | 121.84 ± 3.96 | 93.84 ± 3.96*, ‡ | 28.84 ± 3.96 |

***Table 4. Difference in Mean BP (MBP) of Three Regimens***

Values expressed as Mean ± SD. *$p < 0.05$ versus LST, †$p < 0.05$ versus AMLO, ‡$p < 0.05$ versus (base line SBP of that group)

Table 5. It focuses on the common adverse effects noted the two groups of drugs. Dizziness was observed as the most common adverse effect seen with LST in 3.5% of the cases, followed by headache in 1.5% of the patients. Cough was seen in 0.5% of the patients. Similarly, in the AMLO group pedal oedema ranks highest (10%) amongst adverse effects followed by palpitations (2.2%). Similarly, in the (LST+AMLO) group dizziness ranks highest (0.8%) amongst adverse effects followed by G.I. upset (0.5%).

| Adverse effects | (%) of patients LST group | (%) of patients AMLO group | (%) of patients LST+AMLO group |
|---|---|---|---|
| Dizziness | 3.5% | 1.2% | 0.8 |
| Headache | 1.5% | 0.9% | 0.2 |
| Palpitations | 1.0% | 2.2% | 0.4 |
| G.I. upset | 0.8% | 0.7% | 0.5 |
| Cough | 0.5% | 0% | 0% |
| Emotional distress | 1.0% | 0.8% | 0.2 |
| Pedal edema | 0.6% | 10% | 2 |
| Hot flushes | 0.4% | 0.5% | 0.1 |

***Table 5. List of Adverse Effects Commonly Seen with LST and AMLO***

## DISCUSSION

Meta-analysis of randomized controlled trials has showed that treating systolic blood pressure (SBP) and diastolic blood pressure (DBP) to targets that are <140/90 mmHg is associated with a 30%-40% reduction in stroke risk and reduces the risk of coronary death by 27-35%.[17]

A meta-analysis study by Wang et al examined the effects of Amlodipine and ARBs in the prevention of stroke and MI in patients with HTN.[18] The study included 12 trials of 94,338 patients. The results of this meta-analysis demonstrated that compared with ARBs, Amlodipine reduced the incidence of stroke and MI by 16% and 17% respectively, with better blood pressure control.

The results of our study demonstrated that the fixed combination of amlodipine and losartan has a high antihypertensive efficacy that is sustained in the long term with a quite reduced percentage of loss of blood pressure control.

We observed that, in the long term, more than 60% of the patients treated with the fixed combination of amlodipine and losartan remained with diastolic blood pressure levels equal to or lower than 85 mmHg, thus achieving the goals recommended by current guidelines for the treatment of hypertension.[19] Still regarding antihypertensive efficacy, we observed that when it was assessed using systolic blood pressure normalization alone or in combination with diastolic blood pressure, the percentages obtained were lower than those reported when only diastolic blood pressure was considered for the three therapeutic regimens, reflecting the low efficacy of the drugs available for the treatment of hypertension in reducing and controlling systolic blood pressure. Again, patients treated with the fixed combination of amlodipine and losartan showed the highest rates, which were statistically different from that observed with losartan, not from that reported for patients who received amlodipine alone.

It is important to point out that blood pressure reduction provided by the treatment with the fixed combination of amlodipine and losartan did not cause any secondary increase in sympathetic activity, since no significant variations of heart rate occurred. This fact is beneficial and also helps explain the long-term maintenance of the antihypertensive efficacy with a low rate of loss of blood pressure control. In addition to a high efficacy in reducing blood pressure, keeping it at controlled levels, an antihypertensive drug should also have a good tolerability profile, since the presence of adverse effects may decrease the degree of compliance of the patient to the therapeutic regimen, thus ultimately leading to treatment dropout.[20] Our results demonstrate that the fixed combination of amlodipine at low doses and losartan at higher doses has a very good tolerability profile with a low incidence of adverse events. Moreover, when present, the great majority of these adverse events were mild; given that only for a very small proportion of those who presented with adverse events was treatment discontinuation necessary.

The frequency of adverse events was significantly higher among patients treated with amlodipine alone especially in the long term. In the losartan alone group, as expected[20], we observed a lower incidence of adverse events, confirming the excellent tolerability of this class of antihypertensive drugs. The most frequent adverse events in our study with the fixed combination of amlodipine and losartan, and with the monotherapies were lower extremity oedema and headache.[21] The incidence of lower extremity oedema was particularly significant among patients treated with amlodipine alone, reaching rates higher than 18% in the long term. With the fixed combination of amlodipine and losartan, the incidence of this adverse event was much lower, approximately fourfold less frequent than in the amlodipine alone group.

On one hand, the good tolerability of the combination may be explained by the use of lower doses of each of the hypotensive drugs, since the existence of a strong relation between the dose of the hypotensive drug and the frequency of adverse events is known.[22] On the other hand, the lower incidence of lower extremity oedema observed with the combination – approximately one fourth of that observed in the amlodipine group, results not only from the use of lower doses of this calcium channel antagonist, but also from its synergistic interaction with losartan.

Thus, dihydropyridine calcium antagonists are known to be potent arterial vasodilators, but less effective as venodilators. Moreover, these agents have been demonstrated to be able to cause secondary sympathetic stimulation in varying degrees, thus increasing catecholamine release which ultimately promotes venoconstriction.[21] Consequently, in patients treated with dihydropyridine drugs there would be an increase in hydraulic pressure in the capillary region, exceeding the oncotic pressure with a resulting fluid extravasation into the interstitial space and, therefore, with oedema formation. By gravity action, this oedema tends to be located in the lower extremities, especially in the malleolus region, although even anasarca has already been described in patients using dihydropyridine calcium antagonists. This adverse event of dihydropyridine calcium antagonists has usually a late onset (after six to eight weeks of treatment) and becomes more intense during the day and in the summer.

On the other hand, the dilation effectiveness both arterial and venous of angiotensin II receptor blockers is

well known.[11] Thus, when an ARB is combined with a calcium antagonist venular dilation is facilitated and hydraulic pressure in capillaries is reduced, and consequently the likelihood of oedema formation also decreases. The better tolerability of the combination, as previously mentioned, will surely benefit treatment compliance.[20]

However, patient compliance to treatment is also known to be influenced by countless factors such as the doctor-patient relationship, the knowledge of the disease, the absence of symptoms, the development of adverse events with antihypertensive medication, the number of pills to be taken, and others.[23]

## CONCLUSION

In brief, the results of our study demonstrated that the fixed combination of amlodipine and losartan has a high antihypertensive efficacy, allowing approximately 60% of the patients treated to achieve and maintain, in the long term, the new goal of blood pressure control. The antihypertensive effect of the combination is sustained in the 24 hours, thus allowing its use in a single daily dose, which benefits the compliance to treatment. The tolerability of this fixed combination of antihypertensive drugs is also very good, with a low incidence of adverse events further facilitating compliance.

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