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Original Research

To compare the effectiveness and tolerability of lercanidipine with amlodipine in patients with essential hypertension

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ABSTRACT:

Aim: To compare the effectiveness and tolerability of lercanidipine with amlodipine in patients with essential hypertension. **Material and methods:** A total of 120 patients were included in the trial and randomly assigned to two groups, with 60 patients in each group. Patients in first group received tablet lercanidipine 10 mg while second group patients received tablet amlodipine 5 mg in the beginning, both once daily orally for 12 weeks of duration. Follow up was done at 2, 4, 8 and 12 weeks. At each visit, patients were clinically examined and medical history was noted. All patients advised lifestyle modifications. At each visit heart rate was noted, systolic and diastolic blood pressure (BP) was recorded in sitting position after 10 minutes of rest by auscultation method using mercury sphygmomanometer. The patients were advised to avoid smoking or drinking coffee within 30 minutes before assessment of BP. Laboratory investigations like serum creatinine, SGOT, SGPT, random blood sugar level were carried out at first day and 12 weeks of study. **Results:** The mean reduction in systolic BP in lercanidipine group was 12.00±3.27 mmHg at 2 weeks, 16.4±3.45 mmHg at 4 weeks, 20.77±4.27 mmHg at 8 weeks and 23.6±4.14 mmHg at 12 weeks of treatment (Table 3). While the mean reduction in systolic BP in amlodipine group was 10.95±3.54 mmHg at 2 weeks, 15.79±3.55 mmHg at 4 weeks, 19.95±4.81 mmHg at 8 weeks and 22.81±4.12 mmHg at 12 weeks of treatment. When the reduction in systolic BP in two groups was compared, there was no significant difference between the two groups ($p>0.05$). The mean reduction in diastolic BP in lercanidipine group was 8.17±1.52 mmHg at 2 weeks, 10.8±2.31 mmHg at 4 weeks, 12.44±1.75 mmHg at 8 weeks and 14.26±1.98 mmHg at 12 weeks. While the mean reduction in diastolic BP in amlodipine group was 8.09±1.92 mmHg at 2 weeks, 10.54±2.63 mmHg at 4 weeks, 12.36±2.25 mmHg at 8 weeks and 13.86±2.04 mmHg at 12 weeks. When these values were compared between two groups, the difference was not statistically significant ($p>0.05$). **Conclusion:** Thus, it can be concluded that, for the comparable antihypertensive efficacy, lercanidipine is associated with considerably lower incidence of vasodilation related side effects than amlodipine, especially pedal edema. This favorable tolerability profile can potentially enhance treatment outcome by promoting better adherence to drug therapy.

Keywords: Lercanidipine, Amlodipine, Hypertension,Edema

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INTRODUCTION

Hypertension is a prevalent issue in worldwide healthcare. In recent decades, there has been a notable rise in the occurrence of hypertension in India, particularly among the urban population.[1] It is a well acknowledged risk factor for cardiovascular illnesses.[2] It is a frequent occurrence in individuals with diabetes, which is itself a significant contributor to cardiovascular risk.[3] The Calcium channel blocker (CCB) family of pharmaceuticals consists of three categories of substances that have diverse pharmacodynamic effects. The dihydropyridines category of calcium channel blockers (CCBs) is well acknowledged for its high tolerability and safety profile. They are regarded as one of the first choices for antihypertensive medications. However, the most problematic adverse responses associated with them are the development of pedal edema and other side symptoms connected to vasodilation, such as headache, dizziness, flushing, and palpitation.[4] The low tolerability of this medicine might result in inadequate adherence to the treatment. Research indicates that 25% of patients cease using antihypertensive medication during the first year of treatment due to negative side effects.[5-7] Furthermore, this edema may deteriorate with time, resulting in hyperpigmentation and skin discolouration. This might result in a decrease in dosage or the avoidance of using this very effective category of medications. Lercanidipine is a compound derived from third

generation calcium channel blockers (CCBs). It is said to have the ability to consistently and effectively reduce blood pressure when taken once day. The vasoselective dihydropyridine congener is associated with a low incidence of common adverse medication responses such as pedal edema, headache, dizziness, and palpitation. Only a small number of clinical studies have been carried out to compare this medicine with its older and well-established counterpart, amlodipine. This research was conducted to assess the effectiveness and tolerability of lercanidipine in patients with essential hypertension who were receiving treatment at a tertiary care hospital. The aim was to determine how well the medication worked and how well it was tolerated, taking into account that different populations may have different levels of tolerance to antihypertensive drugs.

MATERIAL AND METHODS

This investigation was conducted at a tertiary care hospital over the course of one year. It was a prospective, randomized, double-blind, parallel-group study that received clearance from the institutional ethics committee. This research included recently diagnosed individuals of both genders, aged 35 years or older, who had mild to moderate essential hypertension (with systolic blood pressure ranging from 140 to 179 mmHg and diastolic blood pressure ranging from 90 to 109 mmHg). These patients were recruited in the trial after providing written permission with full understanding of the information provided. The following patient categories were excluded: patients taking alternative antihypertensive medications, those with secondary hypertension, obstructive biliary disease, cholestasis or hepatic impairment, renal impairment, aortic stenosis, unstable angina, uncontrolled heart failure, and myocardial infarction within the past month, as well as pregnant and lactating women, and female patients of childbearing age who were not using medically approved contraceptives. A total of 120 patients were included in the trial and randomly assigned to two groups, with 60 patients in each group.

Simple randomization was done and allocation was concealed by employing different investigators for each step of random number generation, enrolment, assignment of patients to treatment groups. Participants and investigators were blinded to achieve double blind. Patients in first group received tablet lercanidipine 10 mg while second group patients received tablet amlodipine 5 mg in the beginning, both once daily orally for 12 weeks of duration. Follow up was done at 2, 4, 8 and 12 weeks. At each visit, patients were clinically examined and medical history was noted. All patients advised lifestyle modifications. At each visit heart rate was noted, systolic and diastolic blood pressure (BP) was recorded in sitting position after 10 minutes of rest by auscultation method using mercury sphygmomanometer. The patients were advised to avoid smoking or drinking coffee within 30 minutes before assessment of BP. Laboratory investigations like serum creatinine, SGOT, SGPT, random blood sugar level were carried out at first day and 12 weeks of study. The primary efficacy parameters were the reduction in baseline systolic and diastolic BP. If the patient did not attain the target blood pressure of 140/90 mmHg, the dose was titrated at 4th and 8th weeks by 5mg and 2.5 mg in lercanidipine and amlodipine groups respectively. Patients who did not attain target BP level at the end of study were labelled as non-responders and referred to physician for further treatment. Tolerability and safety was assessed by presence or absence of adverse drug reactions, and derangement of laboratory parameters. Signs and symptoms namely pedal edema, headache, dizziness, flushing, palpitation, fatigue, constipation, nausea, vomiting, muscle cramps, dyspepsia, difficulty in micturition, day time sleepiness, tachycardia and rash were noted.Data was checked for normality. Qualitative data was analysed by using Z test for difference between two proportions or Fisher's exact test for small sample sized data. Quantitative data was analysed using Z test for difference between two means. P value <0.05 was taken as significant and p value <0.001 was considered as highly significant; while p value >0.05 was regarded as non-significant.

RESULTS

Baseline values of all three groups were comparable with respect to age, sex, habits, systolic BP, diastolic BP and heart rate (Table 1).

Table 1: Baseline data of lercanidipine and amlodipine groups

Parameters	Lercanidipine =60	Amlodipine =60	p value
Systolic BP (mmHg)	156.04±9.52	156.81±9.42	p>0.05
Diastolic BP (mmHg)	97.15±4.21	97.5±4.44	p>0.05
Heart rate (bpm)	75.47±5.47	75.22±4.69	p>0.05

In both lercanidipine and amlodipine treated groups, the reduction in systolic BP was found to be highly statistically significant (p<0.001) at 2, 4, 8 and d 12 weeks of therapy, when compared with the baseline readings (Table 2). The reduction in diastolic BP was also found to be statistically significant (p<0.001) at 2, 4, 8 and 12 weeks of therapy, when compared with the baseline readings, in both the groups.

Table 2: Effect of drugs on mean systolic and diastolic blood pressure (mmHg) at 2, 4, 8 and 12 weeks.

Duration	SystolicBP		DiastolicBP	
	Lercanidipine =60	Amlodipine =60	Lercanidipine =60	Amlodipine =60
Day0	156.04±9.52	156.81±9.42	97.15±4.21	97.5±4.44
2weeks	144.04±6.65	145.86±7.11	88.97±3.00	89.40±3.03
4weeks	139.64±6.67	141.02±6.95	86.35±2.67	86.95±2.74
8weeks	135.26±5.84	136.68±6.58	84.71±3.46	85.13±3.21
12 weeks	132.4±5.86	134±6.51	82.88±3.37	83.63±3.43

Table 3: Comparison of mean reduction in systolic and diastolic blood pressure (mmHg) from the baseline

Duration	SystolicBPreduction		Pvalue	DiastolicBPreduction		Pvalue
	Lercanidipine =60	Amlodipine =60		Lercanidipine =60	Amlodipine =60	
2weeks	12.00±3.27	10.95±3.54	p>0.05	8.17±1.52	8.09±1.92	p>0.05
4weeks	16.4±3.45	15.79±3.55	p>0.05	10.8±2.31	10.54±2.63	p>0.05
8weeks	20.77±4.27	19.95±+4.81	p>0.05	12.44±1.75	12.36±2.25	p>0.05
12 weeks	23.6±4.14	22.81±4.12	p>0.05	14.26±1.98	13.86±2.04	p>0.05

Table 4: Adverse drug reactions observed in both the groups

Adverse reactions	Lercanidipine =60	Amlodipine =60
Pedaledema*	1	8
Headache	2	4
Flushing	1	2
Tachycardia	-	1
Dizziness	-	1
Fatigue	1	1
Constipation	-	1
Total number of adverse reactions	5	18

The mean reduction in systolic BP in lercanidipine group was 12.00±3.27 mmHg at 2 weeks, 16.4±3.45 mmHg at 4 weeks, 20.77±4.27 mmHg at 8 weeks and 23.6±4.14 mmHg at 12 weeks of treatment (Table 3). While the mean reduction in systolic BP in amlodipine group was 10.95±3.54 mmHg at 2 weeks, 15.79±3.55 mmHg at 4 weeks, 19.95±4.81 mmHg at 8 weeks and 22.81±4.12 mmHg at 12 weeks of treatment. When the reduction in systolic BP in two groups was compared, there was no significant difference between the two groups (p>0.05). The mean reduction in diastolic BP in lercanidipine group was 8.17±1.52 mmHg at 2 weeks, 10.8±2.31 mmHg at 4 weeks, 12.44±1.75 mmHg at 8 weeks and 14.26±1.98 mmHg at 12 weeks. While the mean reduction in diastolic BP in amlodipine group was 8.09±1.92 mmHg at 2 weeks, 10.54±2.63 mmHg at 4 weeks, 12.36±2.25 mmHg at 8 weeks and 13.86±2.04 mmHg at 12 weeks. When these values were compared between two groups, the difference was not statistically significant (p>0.05).

Table 5: Effect of drugs on laboratory parameters and heart rate.

Parameters	Lercanidipine		P value	Amlodipine		P value
	Before treatment	After treatment		Before treatment	After treatment	
Creatinine(mg/dl)	0.98±0.29	0.91±0.23	p>0.05	1.04±0.21	0.95±0.27	p>0.05
SGPT(IU/L)	21.63±6.97	21.11±6.34	p>0.05	23.29±5.81	23.92±5.51	p>0.05
SGOT(IU/L)	23.48±7.11	24.09±7.24	p>0.05	25.23±6.11	25.98±5.93	p>0.05
BSL(mg/dl)	99.42±8.33	98.42±8.72	p>0.05	98.99±9.94	99.74±8.99	p>0.05
Heartrate(bpm)	75.47±5.45	74.94±3.93	p>0.05	75.22±4.69	74.65±3.28	p>0.05

6 patients in lercanidipine group and 7 patients in amlodipine group not achieved target BP at the end of study. These patients were labelled as non-responders. There was no statistical difference found in number of non-responders between two groups (p>0.05).In lercanidipine treated group, adverse reactions noted were peripheral edema, headache, flushing and fatigue. In addition to these, amlodipine treated patient reported tachycardia, dizziness and constipation. As shown in table 4, 4 patients reported 5 adverse events in lercanidipine treated group as compared to 13 patients showing 18 adverse reactions in amlodipine group. The difference in number of patients reporting adverse reactions between lercanidipine and amlodipine group was foundstatistically significant (p <0.05).3 patients in

lercanidipine group experienced 4 vasodilatory adverse reactions (viz. peripheral edema, headache and flushing) while in amlodipine group 11 patients showed 16 vasodilation related side effects (viz. peripheral edema, headache, flushing, dizziness and tachycardia). In lercanidipine group, 1 patient hadreported pedal edema while 8 patients had showed pedal edema in amlodipine treated group. When two groups were compared, the incidence of pedal edema was significantly higher in amlodipine group ($p<0.05$). There was no significant difference observed in mean blood pressure of patients with or without pedal edema with in both the groups ($p>0.05$). Though numbers of various adverse effects other than pedal edema were more in amlodipine treated group, when this difference was compared, it was found non-significant ($p>0.05$) (Table4).Table 5 shows the values of serum creatinine, SGPT, SGOT, random blood sugar level and heart rate at the baseline and at the end of the study in both the groups. There was no significant differences observed in these values ($p>0.05$) before and after treatment.

DISCUSSION

Controlling high blood pressure, which is a significant risk factor for cardiovascular disease, often requires long-term medication treatment to achieve precise blood pressure management.[8] In order to enhance adherence to the pharmacological therapy, there is a need for antihypertensive medicines that are better tolerated. CCBs have been investigated for their impact on cardiovascular safety. Pedal edema is a frequently documented adverse effect associated with dihydropyridine group of calcium channel blockers (CCBs). Edema is directly proportional to the dosage and may reach levels higher than 80% when extremely large dosages of dihydropyridines are administered.[9] Amlodipine is a well-established and commonly prescribed drug in its class. But different tolerability pattern can be seen between compounds of the same class.[10] Therefore this study was undertaken to compare lercanidipine, a newly added dihydropyridine congener, with commonly used dihydropyridine amlodipine. This study showed that lercanidipine significantly lowered blood pressure within 15 days of the therapy compared to base line in majority of the patients. A consistent increment in the antihypertensive action of lercanidipine was observed throughout study period. When antihypertensive efficacy of lercanidipine was compared with amlodipine, both drugs seem to be equally effective in reducing systolic and diastolic BP. The difference in non-responders between two groups wasalso statistically insignificant.Table 5 shows data related with tolerability of the two drugs in the study. 4 patients reported 5 adverse reactions in lercanidipine treated group as compared to 13 patients showing 18 adverse reactions in amlodipine group. This difference in number of patients reporting adverse reactions between two group was statistically significant ($p <0.05$).

In the study, patients treated with lercanidipine had experienced lower rates of vasodilatory side effects than those who received amlodipine. Among all vasodilation related side effects observed, major difference inincidence was observed in pedal edema. In lercanidipine group, 1patient experience edpedal edema while 8patients reported it in amlodipine treated group. This difference was found to be statistically significant ($p <0.05$). Similar reports have been shown in some of the earlier studies. Leonetti et al. has found significantly higher rates of edema in amlodipine treated group compared to lercanidipine.[10] Observations in another study indicated that for any given fall in blood pressure, the incidence of vasodilatory edema was significantly less with lercanidipine compared with the few second-generation calcium channel blockers including amlodipine.[11] This difference in incidence of edema cannot be related to extent of reduction in blood pressure, as the magnitude of blood pressure reduction is similar in both the groups and no difference in magnitude of antihypertensive effect was observed in patients with or without edema.The edema is outcome of capillary fluid filtration into the interstitial space of the tissue. Normally, postural vasoconstriction occurs in both the arteriolar and the venous limb of the blood vessels when there is a change from the supine to the standing position. This venoarteriolar reflex maintains the capillary fluidfiltration constant. The precapillary arteriolar vasoconstriction is selectively diminished by CCBs. They appear to block the myogenic component of the reflex controlofthe cutaneousbloodflow, whichisindependent of neural, metabolic, and other hormonal influences.[12] This could be responsible for rise in intracapillary pressure, which results in capillary fluid filtration into the interstitium. This leads to formation of edema which seems to be exaggerated by gravity.Lercanidipine seems to have different set of influence on the blood vessels compared to older CCBs. Experimental studies have shown that lercanidipine also has a distinct vasodilatory effect on the efferent arteriole in addition to the afferent arteriole in the kidney.[13] Thus, it was stated that lercanidipine provides a more balanced pre- and postglomerular dilation, thereby reducing intracapillary pressure. It was hypothesized that such a balanced vasodilator action could take place in other capillary beds as well, which results in decreased incidence of the edema.[11]

Some studies have proposed other possible mechanisms. One hypothesis suggests that lercanidipine causes lesser venoconstriction than other drugs due to lower sympathetic activation. Fogari et al. studied thisdifference by estimating serum levels of norepinephrine.It was seen that lercanidipine treated patients showed lesser norepinephrine levels than patients treated with nifedipine GITS.[14] A different effect on vascular permeability and

consequent fluid extravasation has also been suggested.[15] Another hypothesis states that different pattern of pharmacological action of lercanidipine is responsible for its favourable tolerability profile. Lercanidipine proposed to have a greater solubility within the arterial cellular membrane bilayer compared to other long acting dihydropyridines. This results in longer stayin the blood vessels and consequent long duration of action even though it has relatively short plasma half-life. Therefore it was suggested that rapid removal of lercanidipine from plasma may be responsible for its favourable tolerability profile.[16]Though incidence of vasodilation related side effectsother than pedal edema were less in lercanidipine treated group as compared to amlodipine group, the difference was statistically not significant. This observation was similar to the findings ofthe ELYPSE and the ELECTRA study.[17,18]No drug had any adverse impact on the values of serum creatinine, SGPT, SGOT, blood sugar level and heart rate in this study.Apart from the efficacy parameters studied in the present study, various other favourable effects of lercanidipine have been observed in previous studies. Human studies have demonstrated that lercanidipine is equally effectivein young and old patients (especially in isolated systolic hypertension). It is also effective in patients associated with comorbid conditions such as type 2 diabetes and/or renal dysfunction.[2] It is also stated that its stable blood pressure control without marked hypotension during the night hours, which can be related to coronary events and strokes, will promises cardiovascular safety.[19]Therefore, lercanidipine appears to be well tolerated inall age groups with favorable efficacy. Findings of the present study and observations from the previous clinical trials make lercanidipine a flexible choice for antihypertensive treatment across a broad range of patients. Despite its advantages, one disadvantage of lercanidipine is its higher cost compared to amlodipine. The present study is a small study both as regards to the number of patients included and the duration. In India more extensive studies including large number of patients with differing severity and comorbidities; considering more efficacy parameters to evaluate long term effect and compliance are required to determine the exact utility of this drug.

CONCLUSION

Thus, it can be concluded that, for the comparable antihypertensive efficacy, lercanidipine is associated with considerably lower incidence of vasodilation related side effects than amlodipine, especially pedal edema. This favorable tolerability profile can potentially enhance treatment outcome by promoting better adherence to drug therapy.

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