

Comparison of efficacy and safety of cilnidipine and losartan in patients of hypertension with or without diabetes from Gwalior, India

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ABSTRACT

Background: Hypertension (HTN) is the most common cardiovascular disease. The objectives of present study are to investigate the comparison between cilnidipine and losartan with respect to changes in blood pressure (BP) and heart rate (HR) in hypertensive patients with or without type 2 diabetes mellitus (DM).

Methods: We conducted a longitudinal, prospective, open labelled, comparative clinical study of hypertensive patients with or without type 2 DM. Of 161 enrolled hypertensives, 130 completed the study with follow up over a period of one year. Group I (n=34); and Group III (n = 32) patients with type 2 DM received cilnidipine 10-20mg orally OD. Group II (n =33); and Group IV (n = 31) patients with type 2 DM received losartan 50-100mg orally OD. The dosages were adjusted if the magnitude of reduction was insufficient. The parameters were monitored during follow – up at 4, 8 and 12 weeks.

Results: Levels of systolic and diastolic BP and HR significantly decreased with both drugs. However, magnitude of HR reduction was greater with cilnidipine groups as compared to losartan groups with statistically significant difference (group I 70.79±9.21 versus group II 79.42±8.25, p = 0.000 and group III 76.25±7.08 versus group IV 81±7.15, p = 0.010). Of 161 patients, only 1 patient experienced hot flushes from group I.

Conclusions: The present study demonstrated that therapy with cilnidipine can be used safely and effectively in hypertensive patients with or without diabetes. Cilnidipine was equally efficacious in lowering BP, while it more effectively reduced HR as compared to losartan. Cilnidipine can, therefore, be recommended as an alternative especially when there is associated tachycardia.

Keywords: Blood pressure, Cilnidipine, Diabetes, Heart rate, Hypertension, Losartan

INTRODUCTION

Hypertension (HTN) is the most common cardiovascular disease. It is defined conventionally as sustained increase in blood pressure >140/90 mm of Hg.¹ HTN is the leading contributor to global mortality and disability and is increasing in prevalence in the world due to the obesity epidemic and population aging.

Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90-95% of cases are categorized as primary hypertension which means high blood pressure with no obvious underlying medical cause.² The remaining 5-10% of cases categorized as secondary hypertension is caused by other

conditions that affect the kidneys, arteries, heart or endocrine system.

Cardiovascular disease (CVD) is the first and cerebrovascular disease the third leading cause of death in the United States and world.³ The risk of cardiovascular disease, disability and death in hypertensive patients also increases markedly by concomitant diabetes.¹

In recent years, the numbers of patients suffering from both diabetes mellitus (DM) and hypertension have been increasing. Both essential HTN and DM affect the same major target organs and the common denominator of hypertensive/diabetic target organ-disease is the vascular tree. People with coexisting DM and HTN are at

increased risk of developing atherosclerosis, retinopathy, renal failure, and CVD.⁴

Moreover, it has been shown that lowering BP in high risk patients with DM can reduce deaths from strokes, overall mortality, and CVD events and can slow the progression of renal disease in patients with type 2 DM.⁵ Hence, in this study, we are undertaking patients of Hypertension with Diabetes and without Diabetes.

The purpose of treating HTN is to decrease cardiovascular risk, morbidity and mortality rates. Effective pharmacological treatment of patients with strict blood glucose control and anti-hypertensive therapy has been shown to decrease the associated morbidity and mortality. Unfortunately, several surveys indicate that only one third to one half of patients with HTN have adequate blood pressure control.⁶

According to JNC-8 guidelines, calcium channel blockers (CCBs) are now amongst the first line agents of the anti-hypertensive treatment. All conventional available CCBs have L-type calcium channel blocking property, and has a potent blood pressure lowering effect and few adverse effects. While CCB-induced drop in blood pressure often stimulates sympathetic nerve activity, leading to tachycardia. Cilnidipine is a novel and unique 1,4-dihydropyridine derivatives calcium antagonist with potent inhibitory action against not only L-type but also N-type voltage-dependent calcium channels, unlike the other CCBs which have action only on L-type Ca²⁺ channel.⁷ As the N-type Ca²⁺ channel is abundantly expressed in peripheral sympathetic nerve endings cilnidipine reduces excessive release of catecholamine and suppresses not only BP but also the reflective tachycardia in hypertensive patients and also carries the advantage of reduction in the incidence of pedal oedema.⁸⁻¹⁰

Losartan is an Angiotensin (AT₁) receptor blocker. It is now preferred as first line drug for the treatment of HTN, with the advantage of lower incidence of angioedema, rashes and dysgeusia. Several studies have confirmed that Angiotensin receptor blockers are renoprotective in type 2 DM, independent of its BP lowering action. And are approved for the use in HTN, additionally losartan is also approved for diabetic nephropathy and stroke prophylaxis.¹¹ Thus, as such they are commonly prescribed now.

No study has yet reported status of novel CCB, cilnidipine over losartan. Hence, the present work is planned to find efficacy on BP and HR and safety of cilnidipine versus losartan in patients of hypertension with or without diabetes.

METHODS

Approval of protocol and study document was taken from institutional ethical committee before study

commencement. We undertook randomized, prospective, open label, comparative clinical study of total 161 hypertensive patients with or without diabetes in G.R. Medical College, Gwalior. The study was conducted in the outpatient Cardiology clinic from July 2014 to June 2015. Patients were screened for selection criteria.

Inclusion criteria

- Confirmed cases of HTN having systolic (SBP) 140-180 mmHg and/or diastolic blood pressure (DBP) 90-110 mmHg diagnosed by the physician.
- Confirmed cases of HTN with diabetes mellitus diagnosed by the physician.
- The participant could be of either sex.
- The participant must be 30 years and not more than 65 years old.

Exclusion criteria

- Patients of thyrotoxicosis, acromegaly or hypothyroidism
- Patients of Cushing's syndrome, pheochromocytoma, or scleroderma
- Patients of hyperaldosteronism, or of hyperparathyroidism
- Patients of pregnancy induced HTN, eclampsia and pre-eclampsia or HTN due to hormonal contraceptives (with ethynyl estradiol)
- Patients of neurologic disorders, neurofibromatosis, or obstructive sleep apnoea
- Cancers, all HIV or HBs Ag positive patients
- Drugs viz. alcohol, nasal decongestants, NSAIDs, MAO Inhibitors, steroid use, nicotine use
- Fever of unknown aetiology
- Perioperative HTN (that occurs just before, during or after surgery)
- Patients of Severe aortic stenosis, cardiogenic shock, heart failure and hypotension or recent history of unstable angina or MI (myocardial infarction)
- Patients on anti-tubercular therapy, or anti-psychotics

Over a period of 12 months, subjects of either sex fulfilling the selection criteria, with clinically defined cases of essential HTN and HTN with Type 2 DM were enrolled if they provided written informed consent. Then hypertensive patients were randomly allocated into 4 groups.

- Group I (n= 34) - received 10-20mg of cilnidipine orally once daily.
- Group II (n=33) - received 50-100mg of losartan orally once daily.
- Group III (n= 32) - with type 2 DM received 10-20mg of cilnidipine orally once daily.
- Group IV (n = 31) - with type 2 DM received 50-100mg of losartan orally once daily.

Patients were instructed to take their medication in the morning after breakfast. The goal of blood pressure was set at <140/90 mmHg, for patients >60 years <150/90 while for DM patients <130/80 and attempts were made to keep the blood pressure at this level.¹²

Attempts were made to achieve the goal blood pressure by adjusting the dose levels of cilnidipine. If the clinic BP remained high (SBP >140 mmHg or DBP >90 mmHg) or the magnitude of the reduction in BP was insufficient (a decrease in SBP <20 mmHg or a decrease in DBP <10 mmHg), the dose was increased to 20 mg once daily. In group I, in 11 patients while in Group III, in 9 patients the magnitude of reduction was insufficient (a difference in SBP <20mmHg or decrease in DBP <10mmHg). In these patients dose of cilnidipine was increased to 20 mg once daily. Similarly, in losartan group, in 12 patients from group II and in 11 patients from Group IV the dose was increased from 50 to 100mg of losartan. The BP and HR parameters were monitored during follow – up at 4, 8 and 12 weeks. In each visit, blood pressure was measured with the patient resting comfortably, back supported in the sitting position after a 10-15 minute relaxation period. A mercury sphygmomanometer was used for all measurements, with a medium or a large size cuff according to the patient’s arm circumference. Each patient was studied for a maximum of 12 weeks.

Statistical analysis

Values are expressed as the mean±SD. Differences between pre-treatment and post-treatment values within the same group, and also differences between post-treatment values of cilnidipine and losartan groups were examined for statistical significance using the one-tailed paired Student’s t-test. A P-value less than 0.05 denoted the presence of a statistically significant difference.

RESULTS

During the study, of total 161enrolled patients, 31 patients were dropped out. From group I, 9 patients; from group II, 8 patients; from group III, 6 patients while from group IV, 8 patients were dropped out.

Table 3: The pre-treatment and post-treatment BP and HR changes in group I and group II.

BP in mm Hg	Group I (Pre-T/t values)	Group I (Post-T/t values)	P value	Group II (Pre-T/t values)	Group II (Post-T/t values)	P value
SBP	160.58±11.39	126.35±6.11	0.00001	164.3±11.72	128.42±5.14	0.00001
DBP	92.64±7.96	80.11±4.69	0.00001	93.93±6.23	82±3.6	0.00001
HR (bpm)	88.88±10.16	70.79±9.21	0.00001	91.6±9.08	79.42±8.25	0.00001

Values expressed as mean+SD. P value <0.05 is considered as significant. bpm-beats per minute, T/t - Treatment, SBP- systolic blood pressure, DBP -diastolic blood pressure and HR-heart rate.

Table 3 summarizes the pre-treatment and post-treatment blood pressure and heart rate changes in patients of

Table 1: Baseline characteristics of patients of hypertension in Group I (on cilnidipine) and Group II (on losartan).

	Group I (n=34)	Group II (n=33)
Age (years)	52.5±10.2	56.2±8.34
Male (%)	15(44)	16(48.48)
Female (%)	19(56)	17(51.52)
SBP (mmHg)	160.58±11.39	164.3±11.72
DBP (mmHg)	92.64±7.96	93.93±6.23
HR (bpm)	88.88±10.16	91.6±9.08

Values expressed as mean±SD (i.e. standard deviation); bpm-beats per minute , SBP- systolic blood pressure, DBP-diastolic blood pressure and HR -heart rate.

Baseline characteristics

Table 1 summarizes the baseline characteristics of the patients enrolled for this study in essential hypertension groups. Table 2 summarizes the baseline characteristics of the patients enrolled for this study in essential hypertension with type 2 DM groups. There were no significant differences in background factors between the cilnidipine and losartan groups.

Table 2: Baseline characteristics of patients of hypertension with type 2 DM in Group III (on cilnidipine) and Group IV (on losartan).

	Group III (n=32)	Group IV (n=31)
Age (years)	56.9±8.12	57±8.1
Male (%)	22 (68.75)	22 (71)
Female (%)	10 (31.25)	9(29)
SBP (mmHg)	159.31±9.75	164.32±11.66
DBP (mmHg)	92.25±5.27	92.32±5.89
HR (bpm)	92.06±6.89	92.38±7.98

Values expressed as mean + SD (i.e. standard deviation); bpm – beats per minute, SBP- systolic blood pressure, DBP - diastolic blood pressure and HR -heart rate.

Efficacy results

Changes in the Blood Pressure Levels and changes in heart rate.

essential hypertension with cilnidipine (group I) and losartan (group II). There were significant differences in

pre-treatment and post-treatment SBP and DBP parameters.

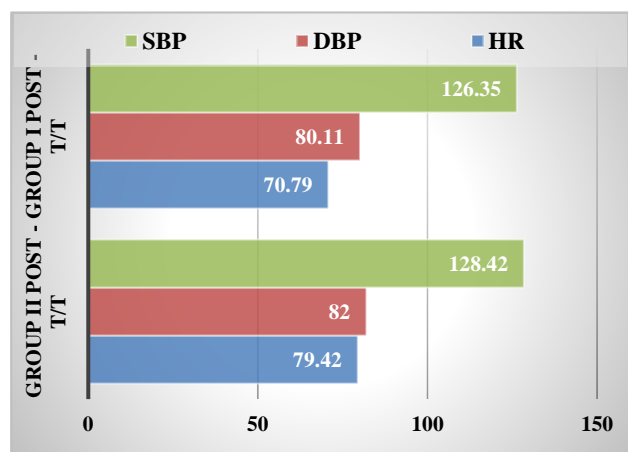


Figure 1: Bar diagram depiction of comparison of post-treatment SBP (systolic blood pressure), DBP (diastolic blood pressure) and HR (heart rate) changes amongst Group I and Group II.

The mean systolic blood pressure, diastolic blood pressure and heart rate of group I decreased by 34 mm of Hg, 12 mmHg and 18bpm respectively after 4 weeks of therapy with Cilnidipine and were statistically significant (p= 0.00001) as compared to pre-treatment values. The mean systolic blood pressure, diastolic blood pressure and heart rate of group II decreased by 36 mmHg, 11 mmHg and 12

bpm respectively after 4 weeks of therapy with Losartan and were statistically significant (p= 0.00001) as compared to pre-treatment values, and these levels continued to decrease until the end of the study. Both cilnidipine and losartan effectively reduced BP and HR.

Figure 1 shows comparison of post - treatment SBP, DBP and HR changes in patients of hypertension amongst group I and group II. There were no significant differences in SBP and DBP between the cilnidipine and losartan groups. But there was significant difference observed in HR values between the two groups.

Table 4 shows the comparison of pre-treatment and post-treatment blood pressure and heart rate changes in patients of hypertension with type 2 DM with cilnidipine (group III) and losartan (group IV).

The mean systolic blood pressure, diastolic blood pressure and heart rate of group III decreased by 30 mm of Hg, 11 mmHg and 16 bpm respectively after 4 weeks of therapy with Cilnidipine and were statistically significant (p= 0.00001) as compared to pre-treatment values. The mean systolic blood pressure, diastolic blood pressure and heart rate of group IV decreased by 33 mmHg, 11 mmHg and 11bpm respectively after 4 weeks of therapy with Losartan and were statistically significant (p= 0.00001) as compared to pre-treatment values, and these levels continued to decrease until the end of the study. Both cilnidipine and losartan effectively reduced BP and HR in diabetic hypertensives as well.

Table 4: Comparison of pre-treatment and post-treatment BP and HR changes in patients of hypertension with type 2 DM with cilnidipine (Group III) and losartan (Group IV).

	Group III (Pre-treatment values)	Group III (Post-treatment values)	P value	Group IV (Pre-treatment values)	Group IV (Post-treatment values)	P value
SBP (mmHg)	159.31±9.75	128.81±7.12	0.00001	164.32±11.66	131.16±7.22	0.00001
DBP (mmHg)	92.25±5.27	81.12±2.91	0.00001	92.32±5.89	81.48±3.79	0.00001
HR (bpm)	92.06±6.89	76.25±7.08	0.00001	92.38±7.98	81±7.15	0.00001

Values expressed as mean+SD (i.e. standard deviation). P value <0.05 is considered as significant.

Table 5: Comparison of post-treatment SBP, DBP and HR changes amongst Group III and Group IV.

	Group III Post T/t (n=43)	Group IV Post T/t (n=41)	P value
SBP (mmHg)	128.81±7.12	131.16±7.22	0.199
DBP (mmHg)	81.12±2.91	81.48±3.79	0.675
HR (bpm)	76.25±7.08	81±7.15	0.010

T/t = treatment. Values expressed as mean±SD (i.e. standard deviation). P value <0.05 is considered as significant.

Table 5 shows comparison of post – treatment SBP, DBP and HR changes amongst group III and group IV. There

were no significant differences in SBP and DBP between the cilnidipine and losartan groups. But there was significant difference observed in HR values between the two groups.

Safety results

Adverse reactions

In our study, of total only 1 patient experienced hot flushes from group I i.e. patients of hypertension on cilnidipine. No specific treatment or drug withdrawal was required in any instance and there were no hospitalizations during the study. Overall no adverse

effects were observed other than this and both the drugs were well-tolerated.

DISCUSSION

This is possibly the first randomized controlled study from India to compare the effectiveness and safety of novel CCB, cilnidipine with standard drug treatment losartan. Epidemiological studies have demonstrated that a higher heart rate is associated with a long term risk of cardiovascular mortality, independent of other cardiac risk factors.¹³ It has been reported that treatment with short acting calcium antagonist may not prevent cardiovascular disease.^{14,15} Accordingly, long lasting CCBs that exert less influence on the sympathetic nervous system are now recommended for treatment of hypertension.¹⁶ A recent clinical trial demonstrated that lowering of BP was associated with a significant fall in cardiovascular event.¹⁷

In recent years, there have been many studies regarding the efficacy of novel CCB, cilnidipine; while, losartan has proven its efficacy and is a standard established treatment for both HTN and HTN with DM. However, there have been no studies investigating the comparison of effect of cilnidipine and losartan. Cilnidipine, a dual L/N-type CCB, has been shown to have a consistent antihypertensive effect without increasing the heart rate because it inhibits the secretion of catecholamine.¹⁸ We thus conducted a special investigation in order to evaluate the safety and efficacy of comparison of losartan and cilnidipine.

In this study once daily use of cilnidipine significantly reduced the BP. We found that cilnidipine and losartan both were equally efficacious in significantly decreasing the BP level. Several studies have reported that once-daily administration of cilnidipine resulted in a safe and more effective BP decrease in essential hypertension without excessive BP reduction or reflex tachycardia.^{19,20}

In the present study, cilnidipine and losartan treatments individually significantly lowered the heart rate from 4 weeks of treatment onward, compared with baseline. However, when compared with each other, magnitude of HR reduction was significantly greater with cilnidipine treatment groups as compared to losartan groups.

Blockade of the neural N-type calcium channel inhibits the secretion of norepinephrine from peripheral neural terminals.⁷ Attenuating norepinephrine release from the sympathetic nerve endings by blocking the N-type calcium channels with cilnidipine might cause a decrease in heart rate. Clinically, Sakata et al. demonstrated by using ¹²³I-metaiodobenzylguanidine cardiac imaging that cilnidipine suppressed cardiac sympathetic over activity while amlodipine had little suppressive effect.⁹

The Framingham Study revealed that heart rates of 75 bpm or more were associated with an abruptly increased

risk for death from cardiovascular events.¹³ Curt et al reported that the reflex increase in sympathetic activity induced by short-acting calcium antagonists may therefore be considered a risk factor for mortality.¹⁴ These findings suggest that it is important to decrease high heart rates during the treatment for hypertension. The data also suggest that the higher the baseline heart rate, the more marked the decrease in heart rate with the use of cilnidipine. Increased sympathetic nervous activity has been strongly implicated in elevated heart rate.²¹ Cilnidipine is considered to decrease the heart rate by blocking the N-type calcium channels in the sympathetic nerve endings, thereby inhibiting norepinephrine release and causing an excessive increase in sympathetic nervous activity.

The study has its share of limitations. Patients < 30 years and >65 years were not included.

Also, the small number of patients studied over a short period of time.

CONCLUSION

This is the first controlled, comparative clinical study to evaluate the safety and efficacy of therapy of cilnidipine versus losartan. The present study demonstrated that cilnidipine was equally efficacious in lowering blood pressure, while it more effectively reduced heart rate as compared to losartan. Therefore, in addition to its antihypertensive effect, cilnidipine carries advantage of reduction in heart rate, thereby protecting the heart from damage associated with cardiovascular causes. Thus, more studies should be carried out and more light should be thrown on this aspect in future.

Notwithstanding the limitations, we can conclude that our data suggest that cilnidipine can be considered a unique CCB that can safely and effectively lower blood pressure and heart rate in patients of essential hypertension with or without diabetes. Cilnidipine can, therefore, be recommended as an alternative especially when there is associated tachycardia.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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