Original Research Paper

Volume : 5 | Issue : 10 | October 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Serum Triglyceride Lowering Effect of Cilnidipine in Patients of Essential Hypertension in Rims, Ranchi

Medical Science

KEYWORDS : Hypertension, Heart rate, Dyslipidemia, Triglyceride, L- and N-type calcium channel blocker, Cilnidipine

Nidhi Singh	Consultant CH Hospital, Dhurwa, Ranchi
*** Manoj Kumar**	Associate Professor, Dept. of Microbiology, RIMS, Ranchi * Correspondence Author
Prakash Kumar	Assistant Professor, Dept. of Cardiology, RIMS, Ranchi
Ashok Kumar Sharma	Assistant Professor, Dept. of Microbiology, RIMS, Ranchi

ABSTRACT

Background*: The relation between Hypertension and Dyslipidemia has been established by many epidemiological studies. Calcium channel blockers are one of the first line drugs for newly diagnosed patients of essential hypertension. Cilnidipine is a new calcium channel blocker act by blocking both L & N type of calcium channel possesses additional beneficial effects apart from lowering blood pressure.*

Method*:The Aim of this study is to evaluate the effectiveness of Cilnidipine in patients of essential hypertension and its effects on lipid profile. Out of 45 enrolled patients 37 completed the study. Cilnidipine started at 10 mg/day, and then adjusted to 5–20 mg/day.*

Results*:After 12 weeks of study patients of showed significant reduction in sBP, dBP, mBP, heart rate and triglyceride from base line (p value < 0.00).*

Conclusion*:In clinical setting where both hypertension and hypertriglyceridemia coexist Cilnidipine can be promising drug of choice.*

Introduction:

Hypertension (HTN) is a chronic medical condition with persistently elevated arterial blood pressure. [1] Around the globe about 1 billion patients are affected by hypertension and the burden is rising owing to escalating obesity and population aging and by 2025 it is projected that about 1.5 billion of patients will be affected worldwide. [2]

Cardiovascular risk factors, including hypertension, tend to co-segregate more commonly than would be expected by chance. Approximately 40% of persons with essential hypertension also have dyslipidemia. Genetic studies have established a clear association between hypertension and dyslipidemia.[3]The term dyslipidemic hypertension (DH) was first used in 1988, in the context of familial DH,[4] which was proposed as a genetic syndrome found in approximately 12% of the patients with essential hypertension and 48% of the hypertensive sib ships.[5] Non-familial forms of DH are more common than the familial ones.Dyslipidemia, a strong predictor of cardiovascular disease,[6] causes endothelial damage,[7-10] and the loss of physiological vasomotor activity that results from endothelial damage may become manifested as increased blood pressure (BP). Therefore, factors like dyslipidemia that cause endothelial dysfunction may lead to hypertension.

Calcium Channel Blockers (CCBs) are one of the first line recommended drug for the treatment of hypertension according to recent "Joint National Committee 8guidelines". [11] CCBs are divided structurally into the dihydropyridine type and the non-dihydropyridine-type. Moreover,various subtypes of Ca^{2+}channels exist, such as L, N, T, P/Q, and R [12, 13].

The N type voltage-dependent calcium channel plays an important role in sympathetic neurotransmission by regulating the release of norepinephrine from sympathetic nerve ending [12]. Cilnidipine is a novel and unique 1, 4-dihydropyridine derivatives calcium antagonist with potent inhibitory action against both L-type and N-type of voltage-dependent calcium channels [13]. It has been reported that once daily administration of Cilnidipine resulted in a safe and more effective lowering of BP in essential hypertension without reflex tachycardia than similar administration of other dihydropyridine calcium antagonist. [14]

The renin-angiotensin aldosterone system (RAAS) promotes atherogenesis. Angiotensin II, a major villain of the RAAS pathway, promotes atherogenesis through stimulation of the angiotensin type 1 receptor (AT1), which increases lipid uptake in cells, vasoconstriction, and free radical production, to foster both hypertension and atherosclerosis.[15]

In animal modelsN-type of CCBs not only suppresses the sympathetic over activity but also have cardioprotective and renoprotective effects. Renin-Angiotensin-Aldosteron (RAAS) system can be suppressed through the sympatholytic actions of N-type of CCBs and thereby they may prevent impaired kidney function. [16]

Blood pressure – lowering drugs have a certain impact on the lipid levels. These changes in lipid levels are important in hypertensives, as up to 40% of the newly diagnosed hypertensives have at least one lipid abnormality.[17] Considering the effect on plasma lipid alpha-blockers, the Renin Angiotensin Aldosterone System (RAAS) blocker or the calcium channel blocker may be the preferred initial therapy in patients with underlying hyperlipidemia.[18]

Currently various groups of antihypertensive drugs are available in the market and therefore selecting the appropriate drug for individual patient is of utmost importance in accordance to patient's clinical profile.

Aims:

The aim of this study is to evaluate the effectiveness of Cilnidipine in patients of essential hypertension and their effects on lipid profile.

Materials and methods:

Study Design

Interventional, randomized, open label, parallel assignment, effectiveness study.

Subjects

We enrolled 45 patients with newly diagnosedessential hypertension along with borderline high lipid profile who presented to outpatient clinic of Cardiology, Rajendra Institute of Medical Sciences (RIMS), Ranchi, during January

2016. Patients were followed up for a period of 12 weeks. Patients were included in the study if they met thefollowing criteria: ≥ 40 years of age of both sex, systolic blood pressure (SBP) / diastolic blood pressure (DBP) of ≥ 140/90 mmHg to ≤ 180/110 mmHg, borderline dyslipidemia not requiring drug treatment (Total Cholesterol – 200-239 mg/dL, and/or Triglyceride – 150-199 mg/dL, and/or LDL – 130-159mg/dL, and/or HDL – 40-60mg/dL.) Patients with secondary hypertension of any causes,angina pectoris or acute coronary artery disease, recent history of congestive heart failure, valvular heart diseases, cardiac arrhythmias, renal dysfunction (serum creatinine level >2.0 mg/dL) and diabetes mellitus were excluded. Pregnant patients and Breast feeding mothers were alsoexcluded. Patients of any existing clinical condition which will not allow safe completion of the protocol and safe administration of study medication were also excluded. Target SBP and DBP were <140 and 90 mmHg, respectively. Eligible study subjects were treated with cilnidipine started at 10 mg/day, and then adjusted to 5–20 mg/day if target BP was not achieved by 4 weeks. If cilnidipine failed to reduce the BP to the target level, then anACE inhibitor and/or ARB were added and these patients were excluded from the study. Duration of follow-up was 12 weeks for each patient. Patients were followed on 2nd, 4th, 8th and 12thweek and at each visit, in office systolic& diastolic Blood pressures and heart rate were recorded. Blood pressure was recorded 3 consecutive times and the average was taken as final value, using mercury sphygmomanometer. 12 hrs Fasting blood samples were taken at baseline and at 12th week between 9am and 11am lipid profile was measured by an automatic biochemical analysis system.

Ethics

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki after receiving approval from the institutional ethical committee of Rajendra Institute of Medical Sciences (RIMS), Ranchi. All subjects provided written informed consent prior to participation.

Statistical analysis

The primary outcomes included changes in heart rate, systolic blood pressure, diastolic blood pressure andlipid profile in hypertensive patients following 12weeks treatment with cilnidipine. Continuous data were presented as mean and standard deviation. We compared values at baseline and after treatment using the 'Z' test. All results were expressed as mean ± SD.p values <0.05 wereconsidered significant. Statistical computations were performedwith Microsoft excel 2014 version.

Results:

Patient characteristics

We analyzed the data of 22 men and 15 women with mean age of 53 years. Out of initially enrolled 45 patients 8 were lost in follow up or excluded from the study due to side effects or inadequate control of blood pressure with study medication by 8th week or due to requirement of lipid lowering drug during the first 4weeks of the study.

Table 1: General Characteristics of Patients of Amlodipine and Cilnidipine Group: -

Parameters	Cilnidipine
N	37
Male	22
Female	15
Age (yrs.)	53.14 (± 5.24)
Body Weight (Kgs.)	67.94 (± 9.59)
Height (cms.)	162.78 (± 7.19)
BMI	25.51(± 2.9)

Table 1 summarizes the baseline characteristics of the patients enrolled for this study. There were no significant differences in background factors between the Amlodipine and Cilnidipine groups.

Table 2: Comparison data (sBP, dBP, mBP, Heart Rate and Lipid Profile)of Base Line and After 12weeks Treatment in Amlodipine and Cilnidipine Group along with corresponding pvalues: -

	Base Line	12th Week	p
sBP	155.38 (± 6.76)	133.38 (± 6.67)	0.00*
dBP	94.16 (± 4.27)	79.92 (± 4.27)	0.00*
mBP	114.48 (± 2.64)	97.71 (± 3.7)	0.00*
Heart Rate	76.96 (± 4.53)	73 (± 3.28)	0.00*
Total Cholesterol	220.51(± 10.72)	218.78(± 9.04)	0.45
Triglyceride	172.46(± 13.42)	162.46(± 10.87)	0.00*
LDL	145.30(± 8.78)	143.97(± 8.05)	0.49
HDL	49.70(± 5.67)	49.27(± 6.55)	0.76

* Significant

Table 2 shows Systolic, Diastolic and Mean BP decreased significantly after treatment with cilnidipine. Heart Rate reduced significantly from base line. In the lipid profile while total cholesterol, LDL and HDL show no significant change, serum Triglyceride level are reduced significantly after 12 weeks of treatment by cilnidipine from the baseline values.

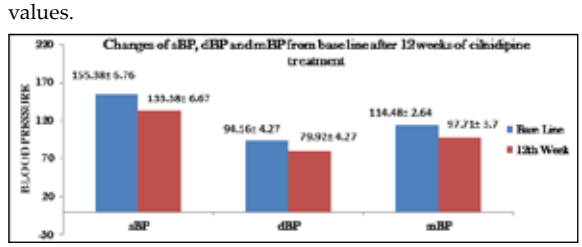


Fig 1: Graphical Representation of Changes of sBP, dBP and mBP from base line after 12 weeks of cilnidipine treatment

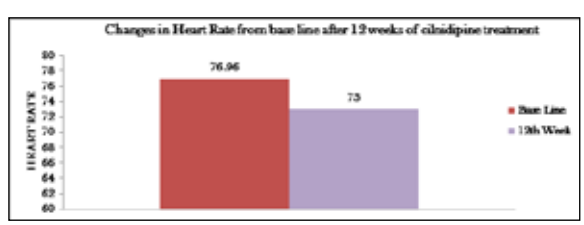


Fig 2: Graphical Representation of Changes in Heart Rate from base line after 12 weeks of cilnidipine treatment

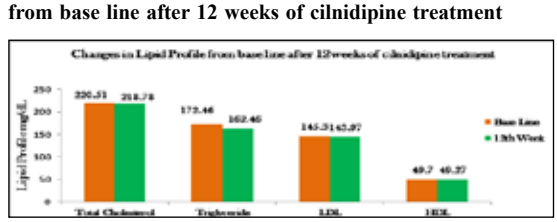


Fig 3: Graphical Representation of variation in lipid profile(Mean ± SD), before and after 12weeks of treatment.

Volume : 5 | Issue : 10 | October 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Discussion:
In the present study, there was significant reduction in office blood pressure readings**(Fig 1)**. Heart rate after 12 weeksof treatment was significantly decreased**(Fig 2)**. Probable explanation for significant reduction of heart rate is due to the inhibition of cardiac sympathetic over activity by blocking L &N type-calcium channel. [19]Similar reduction of Hear Rate in Cilnidipine treated patient has been reported in other studies. [20]High heart rate is aknown independent risk factor for cardiovascular death. Increase mortality from cardiovascular disease in Japanese population [21,22] and in American [23] patients with hypertension has been observed to be associated with a higher heart rate. Reflex tachycardia is a common side effect associated with many dihydropyridine calcium channel blockerswhich actthrough L type of calcium channel only. Replacing these drugs with Cilnidipine a dual L & N type of calcium channel blocker may reduce the heart rate and can potentially reduce the mortality in hypertensive patients.

In this study we showed that after 12 weeks of treatment there is significant reduction in the level of Triglyceride**(Fig 3)**. Similar reduction of Triglyceride was found in hypertensive rats fed with high fat diet and studies done in patients of Type 2 Diabetes with hypertension treated with Cilnidipine [24 - 27]. By blocking the N-type of calcium channels, Cilnidipine, indirectly causes , blockade of the α-receptors and improves the lipid profile by producing peripheral vasodilation, which may facilitate glucose and lipid uptake by muscle cells. Furthermore, α - receptor blockade may also increase the availability of lipoprotein lipase for triglyceride hydrolysis. Blockade of hepatic α-1-adrenoceptors may modulate glycogenolysis and gluconeogenesis, decrease triglyceride output from the liver, reduce cholesterol synthesis, and accelerate binding of LDLs to their hepatic receptors. [28]Although the role of triglycerides as an independent risk factor for CVD has been under debate there is increasing evidence from recent studies demonstrating moderately high triglycerides (150–500 mg/dL) are associated with increased cardiovascular risk. [29] In a recently published meta-analysis involving more than 200,000 patients from 29 studies (including the Reykjavik Study and the EPICNorfolk Study), moderately strong associations were observed between triglyceride concentrations and CHD risk even with low baseline triglyceride concentrations. It has been suggested that the attenuation of the effect of triglycerides on the prediction of future CHD events when HDL cholesterol and other risk factors are included in models is due to the biological variability of triglycerides compared with that of HDL. [30]When this variability is taken into account, triglycerides have greater predictive power on future CHD events. [31]

Cilnidipine by virtue of its triglyceride reducing property may provide better mortality protection in hypertensive patients.

Limitations
Small number of patients is enrolled in this study for a period of 12 weeks only. Therefore, a large number of patients and long term follow up may be needed to confirm the consistency our results.

Conclusion:
Taken together, the results from this study allow us to conclude that cilnidipine (N & L - type CCB) exerts hypotensive activity, on the other hand unlike other dihydropyridine it reduces heart rate and also improve Triglyceride level. Considering these features,cilnidipine is a promising drug of choice for targeting patients with hypertension and hypertriglyceridemia, since both disorders often coexist in clinical setting.

Grants
The study was not supported by any grants or funding agencies.

Conflict of interest
The authors declare no conflict of interest.

References: -

1. Naish, Jeannette; Court, Denise Syndercombe (2014). Medical sciences (2 ed.). p. 562.
2. Lawes CM, Vander HS, Rodgers A: Global burden of blood-pressure-related disease, 2001.Lancet 371:1513, 2008.
3. Selby JV, Newman B, Quiroga J, Christian JC, Austin MA, Fabsitz RR. Concordance for dyslipidemic hypertension in male twins. JAMA. 1991;265: 2079-84.
4. Williams RR, Hunt SC, Hopkins PN, Stults BM, Wu LL, Hasstedt SJ, et al. Familial dyslipidemic hypertension: Evidence from 58 Utah families for a syndrome present in approximately 12% of patients with essential hypertension. JAMA. 1988;259:3579–86.
5. Williams RR, Hopkins PN, Hunt SC, Wu LL, Hasstedt SJ, Lalouel JM, et al. Population-based frequency of dyslipidemia syndromes in coronary-prone families in Utah. Arch Intern Med. 1990;150:582–8.
6. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA. 1987; 257: 2176–2180.
7. Nickenig G. Central role of the AT(1)-receptor in atherosclerosis. J Hum Hypertens. 2002; 16 Suppl 3: S26–S33.
8. Nickenig G, Harrison DG. The AT(1)-type angiotensin receptor in oxidative stress and atherogenesis: Part II: AT(1) receptor regulation. Circulation. 2002; 105: 530–536.
9. Nickenig G, Harrison DG. The AT(1)-type angiotensin receptor in oxidative stress and atherogenesis: Part I: oxidative stress and atherogenesis. Circulation. 2002; 105: 393–396.
10. Niskanen LK, Laaksonen DE, Nyyssönen K et al – Uric acid level as a risk factor for cardiovascular and all cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 2004; 164:1546-1551
11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8).JAMA.
12. Fujii S, Kameyama K, Hosono M, Hyashi Y, Kitamure K. Effect of Cilnidipine, a novel dihydropyridine ca^{+2} channel antagonist on N-type ca^{+2} channel in rat dorsal root ganglion neuron. J PharmacolExpTher 1997; 280:1184-91.
13. Hirning ID, Fox AP, Mc Cleskey FW, et al. Dominant role of N-type ca^{+2} in evoked release of nor- epinephrine from sympathetic neurons. Science 1998; 239:57-61.
14. Feig DI, Rang DH, Johnson RJ – Uric acid and cardiovascular risk. N Engl J Med 2008; 359:1811-1821
15. Iseki K, Oshiro S, TozawaM et al – Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 2001; 24:691-697
16. Uchida et al. - Effects of the N/L-Type Calcium Channel Blocker Cilnidipine on Nephropathy and Uric Acid Metabolism in Hypertensive Patients with Chronic Kidney Disease (J-CIRCLE Study). The Journal of Clinical Hypertension October 2014 | Vol 16 | No 10 | 746-53
17. Ross R. Atherosclerosis an inflammatory disease. N Engl J Med. 1999;340:115–26.
18. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8).JAMA.
19. Bottger A, van Lith HA, Kren V, Krenová D, Bílá V, Vorlícek J, et al. Quantitative trait loci influencing cholesterol and phospholipid phenotypes map to chromosomes that contain genes regulating blood pressure in the spontaneously hypertensive rat. J Clin Invest. 1996;98:856–62.
20. Kannel WB, Carter BL. Initial drug therapy for hypertensive patients with hyperlipidemia. Am Heart J.1989;118:1012.
21. Fujii S, Kameyama K, Hosono M, Hyashi Y, Kitamure K. Effect of Cilnidipine, a novel dihydropyridine ca^{+2} channel antagonist on N-type ca^{+2} channel in rat dorsal root ganglion neuron. J PharmacolExpTher 1997; 280:1184-91.
22. Hirning ID, Fox AP, Mc Cleskey FW, et al. Dominant role of N-type ca^{+2} in

evoked release of nor- epinephrine from sympathetic neurons. Science 1998; 239:57-61.

23. Hoshide S, Kario K, Ishikawa J, et al. Comparison of the effects of Cilnidipine and Amlodipine on ambulatory blood pressure. Hypertens Res 2005; 28:1003-8.
24. Dangi NB et al. Effect of Amlodipine, Cilnidipine and Diltiazem on lipid profiles of hypertensive rats fed with high fat diet: A com-parative study, Bulletin Facult Pharmacy Cairo Univ (2016), 1-7
25. Masuda T, Ogura MN. Beneficial effects of L- and N-type calcium channel blocker on glucose andlipid metabolism and renal function in patients with hypertension and type II diabetes mellitus.CardiovascTher., 2011, 29; 46-53.
26. Ahaneku JE, Sakata K. Effects of Cilnidipine on lipids, lipoproteins and fibrinolytic system inhypertensive patients. Drugs ExpClin Res., 2000, 26; 119-123.
27. Sharp RP, Sirajuddin R, Sharief IM. Impact of carvedilol on the serum lipid profile. Ann Pharmacother 2008; 42:564–71.
28. ShravanthiManthri*, DussaVeena, Ramesh babuAmbari,GoverdhanPuchchakayala. A Prospective Interventional Study on Clinical Effects ofCilnidipine in Hypertensive Patients. IJPRIF 2015; Vol.8, No.10, 70-76
29. Skulas-Ray AC, West SG, Davidson MH, KrisEtherton PM. Omega-3 fatty acid concentrates in the treatment of moderate hypertriglyceridemia. ExpOpinPharmacother 2008; 9:1237–48.
30. Jeppesen J, Hein H, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. Circulation 1998; 97:1026–36.
31. Durrington PN. Triglycerides are more important in atherosclerosis than epidemiology has suggested. Atherosclerosis 1998; 141:S57–62.