Original Research Paper

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

Effects of Cilnidipine on Heart Rate and Uric Acid Metabolism in Patients of Essential Hypertension – in Tertiary Care Hospital

Medical Science

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

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

ABSTRACT

***Background**: The Relation Between Hypertension And Hyperuricemia Has Been Established By 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.*

***Method**:the Aim Of This Study Is To Compare The Effectiveness Of Amlodipine And Cilnidipine In Patients Of Essential Hypertension And Their Effects On Heart Rate And Serum Uric Acid Levels. Out Of 100 Enrolled Patients 92 Completed The Study. They Are Randomly Assigned To Amlodipine (N= 47) And Cilnidipine (N= 45) Groups. Cilnidipine (Started At 10 Mg/Day, Then Adjusted To 5–20 Mg/Day) And Amlodipine (Started At 5 Mg/Day, Then Adjusted To 2.5–10 Mg/Day).*

***Results**:after 24Th Weeks Of Study Patients Of Cilnidipine Groups Showed Significant Reduction In Heart Rate And Serum Uric Acid Levels From Base Line (P Value = 0.00).*

***Conclusion**:in Clinical Setting Where Both Hypertension And Hyperuricemia 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]Hyperuricaemia affects 2 to 18% of the population with varying relation to age, sex, ethnicity and other epigenetic factor and can be regarded as a common metabolic disorder. [3]

Many epidemiological studies confirm the relationship between the Serum Uric Acid (SUA) level and various cardiovascular diseases, such as arterial hypertension, acute and chronic heart failure, stroke, and atherosclerosis. Not only in the patients of frank hyperuricemia (defined by SUA >7 mg in men and > 6mg in women), but also similar relationship is evident in patients with high normal values of SUA (defined by SUA > 5.5 mg/dl) [4, 5]. It has been reported that 25-40% of patients with untreated HTN and more than 80% of patients with malignant HTN have high SUA levels [6].

The net balance between uric acid production and excretion is reflected as the SUA level. Renal insufficiency is a common cause of increase in SUA and long standing untreated hypertensive patients are at risk of developing chronic kidney disease (CKD). Hyperuricemia is highly prevalent in CKD, reflecting the reducing renal excretion of SUA. [6]It hasbeen long known that hypertension is closely related to CKD and both conditions serve as risk factors for various cardiovascular diseases.Moreover sympathetic hyperactivity in hypertensive patients and reduced nitric oxide production in the vascular endothelium caused by insulin resistance in hypertensive patients can lead to increase production of hypoxanthine in the skeletal muscle, resulting in so-called myogenic hyperuricemia. [7]

Calcium Channel Blockers (CCBs) are one of the first line recommended drug for the treatment of hypertension according to recent "Joint National Committee 8guidelines". [8]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 [9, 10].

The N type voltage-dependent calcium channel plays an important role in sympathetic neurotransmission by regulating the release of norepinephrine from sympathetic nerve ending [11]. 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 [12]. 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. [13] 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. [14]

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 compare the effectiveness of Amlodipine and Cilnidipine in patients of essential hypertension and their effects on heart rate and serum uric acid levels.

Materials and Methods:

Study Design

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

Subjects

We enrolled 100 patients with newly diagnosedessential hypertension 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 6 months. 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. Patients with sec-

ondary 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 randomly allocated to two groups and treated with cilnidipine (started at 10 mg/day, then adjusted to 5–20 mg/day) or amlodipine (started at 5 mg/day, then adjusted to 2.5–10 mg/day). If cilnidipine or amlodipine 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 6months for each patient. Patients were followed on 2nd, 4th, 8th, 12th and 24thweek 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. Blood samples were taken at baseline, 12th week and 24th week between 9am and 11am and were immediately placed on ice and centrifuged within 1 h on first visit, 12th and 24th week.Uric acid 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 pulse rate, systolic blood pressure, diastolic blood pressure and serum uric acid in hypertensive patients following 24weeks treatment with amlodipine or 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 48 men and 44 women with mean age of 53 years. Three patients of amlodipine group and five patients of cilnidipine group 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.

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 1: Patient Characteristics: -

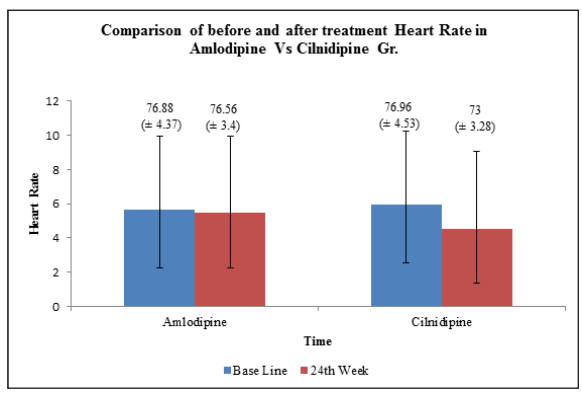
Parameters	Amlodipine	Cilnidipine
N	47	45
Male	25	23
Female	22	22
Age (yrs.)	52.86 (± 5.81)	53.14 (± 5.24)
Body Weight (Kgs.)	67.56 (± 10.85)	67.94 (± 9.59)
Height (cms.)	162.22 (± 6.79)	162.78 (± 7.19)
BMI	25.01(± 5.1)	25.51(± 2.9)

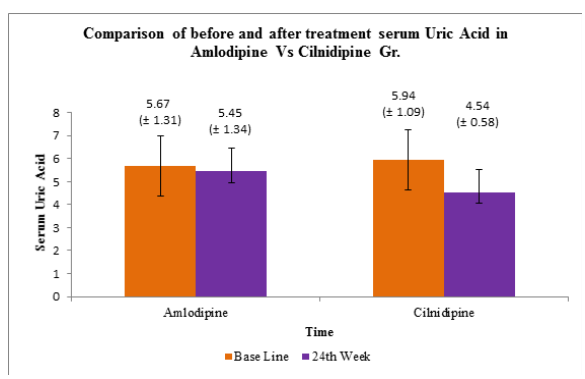
Table 2 Systolic, Diastolic and Mean BP decreased significantly in both groups after treatment. There were no significant differences in the reduction in any of the BP parameters between Amlodipine and Cilnidipine group. Heart Rate reduced significantly from base line in Cilnidipine group after 24 weeks of treatment. Serum Uric Acid also shows significant reduction after 24 weeks of treatment in Cilnidipine group.

Table 2: Comparison of Base Line and After Treatment Values: -

	Amlodipine				Cilnidipine			
	Base Line	24th Week	Z	p	Base Line	24th Week	Z	p
sBP	155.65 (± 7.29)	133.38 (± 6.39)	19.48	0.00@	155.38 (± 6.76)	133.38 (± 6.67)	19.23	0.00@
dBP	93.32 (± 3.97)	78.32 (± 4.22)	18.29	0.00@	94.16 (± 4.27)	79.92 (± 4.27)	16.66	0.00@
mBP	113.83 (± 2.92)	96.45 (± 3.52)	26.76	0.00@	114.48 (± 2.64)	97.71 (± 3.7)	26.09	0.00@
Heart Rate	76.88 (± 4.37)	76.56 (± 3.4)	0.40	0.68	76.96 (± 4.53)	73 (± 3.28)	4.99	0.00@
Uric Acid	5.67 (± 1.31)	5.45 (± 1.34)	0.88	0.37	5.94 (± 1.09)	4.54 (± 0.58)	4.28	0.00@

@ Significant





Discussion:

In the present study, both in Amlodipine group and Cilnidipine group there was significant reduction in office blood pressure readings and extent of reduction in blood pressure is comparable in both the groups. Although changes in heart rate after 6 months of treatment from base line was not significant in Amlodipine group the heart rate was significantly decreased in patients treated with Cilnidipine. Probable explanation for significant reduction of heart rate in Cilnidipine group is due to the inhibition of cardiac sympathetic over activity by blocking L &N type-calcium channel. [15]Similar reduction of Hear Rate in Cilnidipine group in comparison to Amlodipine has been reported in other studies. [16]High heart rate is aknown independent risk factor for cardiovascular death. Increase mortality from cardiovascular disease in Japanese population [17,18] and in American [19] patients with hypertension has been observed to be associated with a higher heart rate.

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

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.

Hypertension and Chronic Kidney Disease (CKD) are closely related and both serve as independent risk factor for various cardiovascular diseases. Hyperuricemia has also been reported to be involved in hypertension and is a major risk factor in progression of CKD in addition to proteinuria. [20, 21]Therefore, while treating hypertension, it is desirable to use appropriate antihypertensives which have no adverse effect on uric acid metabolism.

In this study we showed that after 24weeks of treatment there is significant reduction in the level of SUA in Cilnidipine group. Studies of Hamada et al. reported significant decrease in the serum uric acid level and increased urinary nitrogen monoxide synthesis in hypertensive patients after treatment with Cilnidipine. [22] Improvement of uric acid metabolism in hypertensive patients with chronic kidney disease receiving Cilnidipine has been observed in study by Uchida et al. [7]

Animal study demonstrated suppression of hyperactivity of renal sympathetic nervous system by cilnidipine, which leads to intense dilatation of both afferent and efferent arterioles and a consequent reduction of glomerular filtration pressure. [23]Otherstudies showedsuppression of renin, angiotensin, and aldosterone secretion by cilnidipine. [24,25] In experimental study design using spontaneously hypertensive rats' cilnidipine showed suppression of renin-angiotensin-aldosterone system (RAAS) activity and podocyte disorder. [26] Even clinically in the CARTER study and a trial involving switchingfrom amlodipine to cilnidipine in patients with type 2 diabetes mellitus showed improvement in proteinuria by cilnidipine. [27]

Serum uric acid reduction by Cilnidipine may have several possible mechanisms. Firstly, suppression of sympathetic over activity may suppress the uric acid precursor hypoxanthineformation. This is supported by evidence of suppression of sympathetic hyperactivity by α_1–blockers and Angiotensin Converting Enzyme inhibitors, leading to reduce production of hypoxanthine in the skeletal muscle, thus leading to improvement of myogenic hyperuricemia as seen in study by Ohtahara A et al.[28]Secondly, cilnidipine by restoringblood flow to the skeletal muscle inhibits muscular AMP deaminase activity involved in ATP production, leading to suppressed degradation of AMPto hypoxanthine. [7] Improvement of renal blood flow due to afferent arteriolar dilatation [29] may lead to enhanced excretion of uric acid. In the proximal convoluting tubules, a decrease in filtration fraction (i.e. – glomerular filtration rate divided by renal plasma flow) eventually cause increased uric acid excretion. [27,30]Lastly, the intestinal excretion of uric acid should also be considered. ABCG2 transporters mediate the intestinal excretion of uric acid. Single nucleotide polymorphisms (SNP) of these transporters are found in substantial proportion gout patients.[31] In animal models in face of impaired kidney function, increased expression of ABCG2 transporters are observed as a compensatory mechanism to reduced urinary uric acid excretion. [32]

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

Limitations

There are several limitations in this study. First, the small number of patients is enrolled in this study. Therefore, a large number of patients are needed to confirm our results. Second, the activity of renin–angiotensin–aldosterone system and hypoxanthine were not evaluated in the present study. Third, further study on effect of cilnidipine on intestinal uric acid transporters is needed.

Conclusion:

Taken together, the results from this study allow us to conclude that cilnidipine (N & L - type CCB) exerts hypotensive activity, similar to the L-type CCB amlodipine, on the other hand unlike amlodipine it reduces heart rate and also improve uric acid metabolism. Considering these features,cilnidipine is a promising drug of choice for targeting patients with hypertension and hyperuricemia, 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. Adriana Iliesiu, AlexandruCampeanu, DinuDusceac, et al. Serum uric acid and cardiovascular disease. Maedica, A Journal of Clinical Medicine, 2010; Volume 5 No.3
4. 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
5. Feig DI, Rang DH, Johnson RJ – Uric acid and cardiovascular risk. N Engl J Med 2008; 359:1811-1821
6. 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
7. 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
8. 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.
9. 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.
10. 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.
11. 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.
12. Minami J, Ishimitsu T, Kawano Y, Numabe A, Matsuoka H. Comparison of 24-hour blood pressure, heart rate and autonomic nerve activity in hypertensive patients treated with Cilnidipine or Nifedipine retard. J CardiovascPharmacol 1998; 32:331-6.
13. Minami J, Ishimitsu T, Kawano Y, Numabe A, Matsuoka H. Comparison of 24-hour blood pressure, heart rate and autonomic nerve activity in hypertensive patients treated with Cilnidipine or Nifedipine retard. J CardiovascPharmacol 1998; 32:331-6.
14. Yutaka Mori et al, Additive effects of cilnidipine, an l-/n-typecalcium channel blocker, and an angiotensin iireceptor blocker on reducing cardiorenaldamage in Otsuka long-evans Tokushima Fatty rats with type 2 diabetes mellitus; Drug Design, Development and Therapy 2014:8
15. Sakata K, Shirotani M, Yoshida H, et al: Effectsof amlodipine and cilnidipine on cardiacsympathetic nervous system andneurohormonal status in essentialhypertension. Hypertension 1999; 33: 1447 –1452.
16. Hoshide S, Kario K, Ishikawa J, et al:Comparison of the effects of cilnidi-

pine andamlodipine on ambulatory blood pressure.Hypertens Res 2005; 28: 1003 – 1008.

17. Okamura T, Hayakawa T, Kadowaki T, et al:Resting heart rate and cause-specific death in a16.5-year cohort study of the Japanese general-population. Am Heart J 2004; 147: 1024 – 1032.
18. Hozawa A, Ohkubo T, Kikuya M, et al:Prognostic value of home heart rate forcardiovascular mortality in the generalpopulation: the Ohasama study. Am J Hypertens2004; 17: 1005 – 1010.
19. Gillman MW, Kannel WB, Belanger A, et al:Influence of heart rate on mortality amongpersons with hypertension: the FraminghamStudy. Am Heart J 1993; 125: 1148 – 1154.
20. Heinig M, Johnson RJ. Role of uric acid in hypertension, renaldisease, and metabolic syndrome. Cleve Clin J Med. 2006;73:1059–1064.
21. Krishnan E, Kwoh CK, Schumacher HR, Kuller L. Hyperuricemia and-incidence of hypertension among men without metabolic syndrome.Hypertension. 2007;49:298–303.
22. Hamada T, Yamada K, Mizuta E, Watanabe A, Osaki T, IshidaK, Hasegawa A, Sakata S, Mishima M, Ogino K, Nosaka Y,Miyazaki S, Ohtahara A, Ninomiya H, Kato M, Yoshida A, TaniguchiS, YamamotoK, Hisatome I (2012) Effectsof cilnidipineonserum uric acid leveland urinary nitrogen monoxide excretioninpatients with hypertension.ClinExpHypertens 34:470–473
23. Konno Y, Kimura K. Vasodilatory effect of cilnidipine, an L-type andN-type calcium channel blocker, on rat kidney glomerular arterioles.Int Heart J. 2008;49:723–732.
24. Konda T, Enomoto A, Aritomi S, et al. Different effects of L/N-typeand L-type calcium channel blockers on the renin-angiotensin-aldosterone system in SHR/Izm. Am J Nephrol. 2009;30:155–161.
25. Aritomi S, Wagatsuma H, Numata T, et al. Expression of N-typecalcium channels in human adrenocortical cells and their contributionto corticosteroid synthesis. Hypertens Res. 2011;34:193–201.
26. Fan YY, Kohno M, Nakano D, et al. Cilnidipine suppresses podocyteinjury and proteinuria in metabolic syndrome rats: possible involvementof N-type calcium channel in podocyte. J Hypertens.2010;28:1034–1043.
27. Fujisawa T, Ikegami H, Noso S, et al. Renoprotective effect of N-type-Ca channel blockade in diabetic nephropathy. J Diabetes Complications.2007;21:252–257.
28. Ohtahara A, Hisatome I, Yamamoto Y, et al. The release of thesubstrate for xanthine oxidase in hypertensive patients was suppressedby angiotensin converting enzyme inhibitors and alpha1-blockers.J Hypertens. 2001;19:575–582.
29. Zhou X, Ono H, Ono Y, et al. N- and L-type calcium channelantagonist improves glomerular dynamics, reverses severe nephrosclerosis,and inhibits apoptosis and proliferation in an l-NAME/SHRmodel. J Hypertens. 2002;20:993–1000.
30. Fujita T, Ando K, Nishimura H, et al. Antiproteinuric effect of thecalcium channel blocker cilnidipine added to renin-angiotensininhibition in hypertensive patients with chronic renal disease. KidneyInt. 2007; 72:1543–1549.
31. Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urateexcretion is a common cause of hyperuricemia. Nat Commun.2012; 3:764. doi: 10.1038/ncomms1756.
32. Yano H, Tamura Y, Kobayashi K, et al. Uric acid transporter ABCG2is increased in the intestine of the 5/6 nephrectomy rat model ofchronic kidney disease. ClinExpNephrol. 2014; 18:50–55.