Original article

Comparison of the effects of L-type calcium channel antagonist Amlodipine with L/N-type calcium channel antagonist Cilnidipine on blood pressure, heart rate, proteinuria and lipid profile in hypertensive patients

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Abstract:

Background: Cilnidipine is a novel and unique 1,4-dydropyridine derivative calcium antagonist that exerts potent inhibitory actions not only on L-type but also on N-type voltage dependent calcium channels. Blockade of the neural N-type calcium channel inhibits the secretion of norepinephrine from peripheral neural terminals and depresses sympathetic nervous system activity. ***Objective and methods***: The purpose of this study was to assess the effect of Cilnidipine and Amlodipine on blood pressure (BP) levels. We did BP monitoring before and after once-daily use of Cilnidipine and Amlodipine in 100 hypertensive patients. ***Results***: Both drugs significantly reduced systolic BP (SBP) and diastolic BP (DBP). However, the reductions in pulse rate (PR) were significantly greater in the Cilnidipine group than the Amlodipine group. N-type calcium channel blockade by Cilnidipine may not cause reflex tachycardia, and may be useful for hypertensive treatment. ***Conclusion***: There was significant reduction in proteinuria with Clindipine as compared to Amlodipine. However, there were no significant change in total cholesterol level in diabetes and non-diabetics in both the group.

Keywords: calcium channel antagonist; cilnidipine; amlodipine; hypertension; proteinuria; pulse rate (PR); systolic BP (SBP); diastolic BP (DBP)

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Introduction:

Hypertension is a widespread public health problem and a major risk factor[1] for damage to heart, kidney, brain, vasculature and other organs resulting in premature morbidity and death[2]. Many studies have reported that calcium antagonists or the combination of a calcium antagonist and an angiotensin blocker improves target organs damage and the clinical outcome in patients with hypertension[31-36]. Dihydropyridine calcium antagonists have been widely used for the treatment of hypertension in Japan[37-38]. Amlodipine avoids sympathetic overactivity or reflex tachycardia because it has a longer biological half-life than short-acting calcium antagonists. Studies using ambulatory blood pressure (ABP) monitoring have demonstrated that amlodipine controls BP levels throughout a 24-h period[39, 40]. 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.[3] The N type voltage-dependent calcium channel plays an important role in sympathetic neurotransmission and regulates the release of norepinephrine from sympathetic nerve ending.[4] It has been 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 than similar administration of other dihydropyridine calcium antagonist.[5] Akira Takara showed that plasma norepinephrine concentration, a sensitive marker of sympathetic nerve activity, is a significant prognostic marker

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of mortality in congestive heart failure patients[6]. De Champlain showed a sustained rise in blood norepinephrine levels by more than 50% after chronic therapy of Amlodipine[7]. The inhibitory effect on the N-type ca²+ channel by Cilnidipine may bestow an additional clinical advantage for the treatment of hypertension, such as suppression of reflex tachycardia. In morning, arousal from sleep is associated with rise in plasma epinephrine. Cilnidipine due to its sympathetic inhibitory action was more effective than Amlodipine therapy in controlling morning BP in hypertensive patients.[9] In spontaneously hypertensive rats (SHR) treated with N-w-nitro-L-arginine-methylester (L-NAME), Cilnidipine dilates afferent and efferent arterioles in the kidney and decrease glomerular capillary pressure, thereby decreasing proteinuria and improving glomerulosclerosis.[10] In addition a comparative study of Cilnidipine and an ACEI benazepril, has shown that both regimens similarly reduced urine albumin.[11] Cilnidipine a dual L-and N-type calcium channel blocker may be useful for patients with hypertension and diabetes mellitus from its effects on lipid metabolism and renal function.[12] Previous reports indicates beneficial effect of Cilnidipine on lipid profile in addition to the antihypertensive activity.[13,14]

Methods:

Study design: We undertook randomized, open label comparative study of two groups of hypertensive patients between June 2013 to December 2013. Total 100 patients were recruited for this study. One group comprising of 50 patients were taking 5-10mg Amlodipine and other group comprising of 50 patients were taking 10-20 mg Cilnidipine. In Amlodipine group, 20 patients and in Cilnidipine group, 25 patients were diabetic. The numbers of proteinuric patients were 12 and 14 in Amlodipine and Cilnidipine group respectively.

Study procedure: After taken written informed consent patients were screened for selection criteria. Cilnidipine was administered orally at the dose of 10mg. In 10 patients the magnitude of reduction was insufficient (a difference in SBP < 20mmHg or decrease in DBP < 10mmHg). In these patients dose was increased to 20 mg once daily. Amlodipine was administered orally once daily at the dose of 5mg. In 20 patients dose was increased to 10mg once daily when BP was not successfully controlled. BP and Pulse rate were monitored. In proteinuric patient's urinary protein content were standardized for urinary excretion of 1g creatinine. Values represent the mean of two measurements of each time points during the observation period. Serum concentration of total cholesterol, HDL-C, LDL-C and TG were determined by the enzymatic methods with an autoanalyzer. All DM patients in this study were diagnosed as type 2. Dyslipidemia was defined on the basis of abnormal lipid level LDL-Cholesterol (LDL-C) ≥140mg/dl, HDL-Cholesterol(HDL-C) < 40mg/dl, Triglyceride (TG) ≥ 150mg/dl).

Statistical Analysis*:* Values were expressed as the mean±SD. The difference of the baseline characteristics and change in BP and PR parameter between the Amlodipine and Cilnidipine groups was compared using an unpaired t-test. The difference between the values before and after antihypertensive medication within the same group was tested using a paired t-test. P-value < 0.05 considered statistically significant.

Research design and protocol of this study was approved by Ethics Committee of MMIMSR.

Results:

Table 1 summarizes the baseline characteristics of the patients enrolled for this study. There were

Table 1: The baseline characteristics of the patients

	Amlodipine (n=50)	**Cilnidipine (n=50)**
Male (%)	70	58
Age (years)	60 (±4)	64 (±5)
No. with diabetes	22	18
No. with proteinuria	15	12
BMI (Kg/m²)	24±3	24±2
SBP (mmHg)	160±11	160±12
DBP(mmHg)	94±9.8	90±9
PR (bpm)	78±9	76±6.4

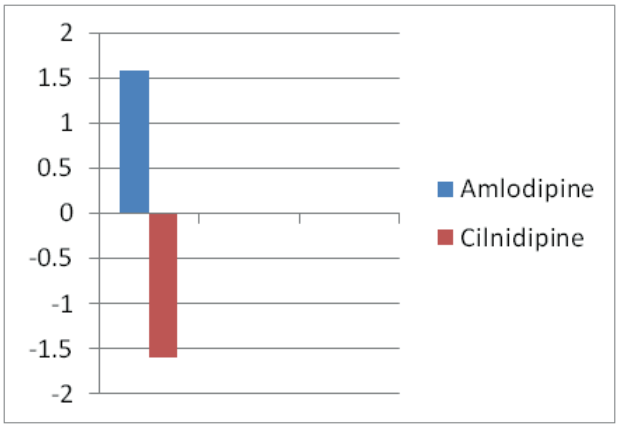

Figure 1: shows the effect of Amlodipine and Cilnidipine on the PR levels. In the Amlodipine group, PR after treatment was significantly higher than that before treatment

Table 2: Blood Pressure Before and After Treatment

	Amlodipine			**Cilnidipine**		
	Before	After	P	Before	After	P
SBP (mmHg)	160±11	146±10	<0.001	160±12	148±11	<0.005
DBP(mmHg)	94±9.8	86±7.4	<0.001	90±9	82±10	<0.001

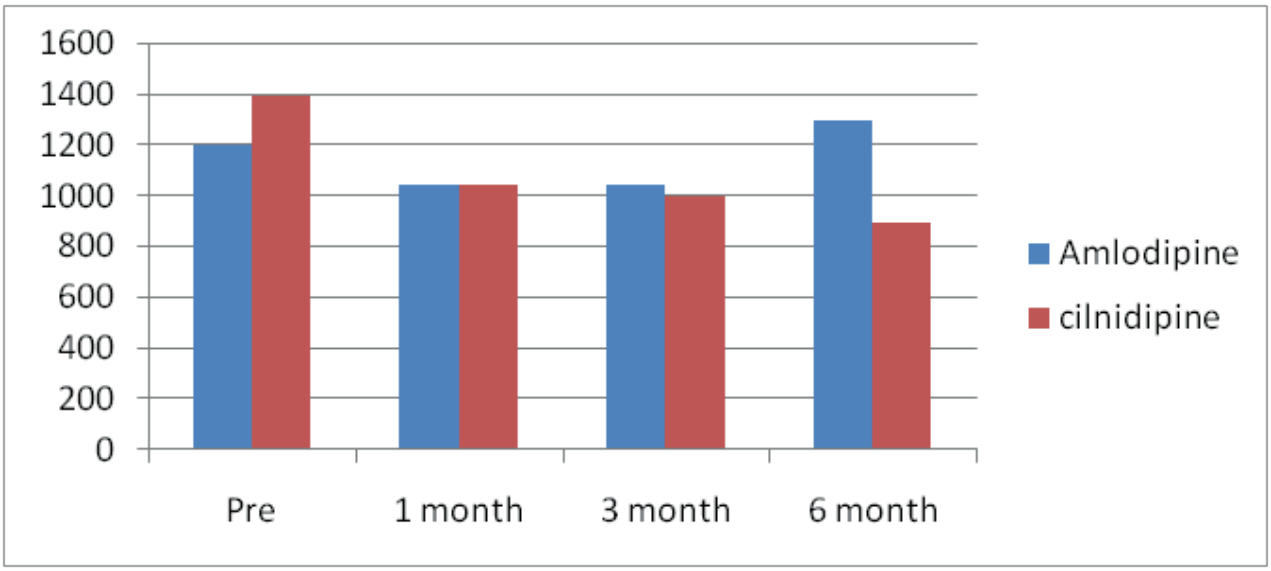

Figure 2: shows the effect of Amlodipine and Cilnidipine on excretion of protein after treatment. The protein/creatinine ratio was significantly lower with Cilnidipine than Amlodipine group

no significant differences in background factors between the Amlodipine and Cilnidipine groups. 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 (Table 2)

Figure 3 & 4 show the effect of Amlodipine and Cilnidipine on lipid metabolism after treatment. There were no significant differences between the Amlodipine treatment and Cilnidipine treatment in terms of total cholesterol, HDL-c and LDL-c level when the analysis was performed on the entire population, the DM(+) or the DM(-) group. TG was significantly higher with Amlodipine treatment in the DM (+) group than in the DM(-) group, while this parameter did not differ significantly with Cilnidipine treatment between the DM(+) group and the DM(-).

Discussion:

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.[15] It has been reported that treatment with short acting calcium antagonist may not prevent cardiovascular disease.[16,17] Accordingly, long lasting calcium channel blockers that exert less influence on the sympathetic nervous system are now recommended for treatment of hypertension.[18] A recent clinical trial demonstrated that lowering of BP was associated with a significant fall in cardiovascular event.[19]

In this study once daily use of Amlodipine or Cilnidipine significantly reduced the BP. We found that Cilnidipine but not Amlodipine significantly decreased the BP level without causing an increase in PR. There have been previous reports that compared the effects of Amlodipine and Cilnidipine.[20, 21] There was a significant negative correlation between the degree of SBP change and that of PR change after Cilnidipine treatment. This finding is an agreement with several previous studies[22, 23] in which Cilnidipine suppressed sympathetic nervous activity, especially under a stress-induced hyperactive condition.

Blood pressure control is important in suppressing the onset of renal dysfunction.[24] It was reported that antihypertensive therapy suppressed the progression of renal dysfunction[25]. Regarding glomerular kinetics, it has been shown that inhibition of angiotensin II suppress the elevation of glomerular pressure. Among CCBs, Cilnidipine has been reported

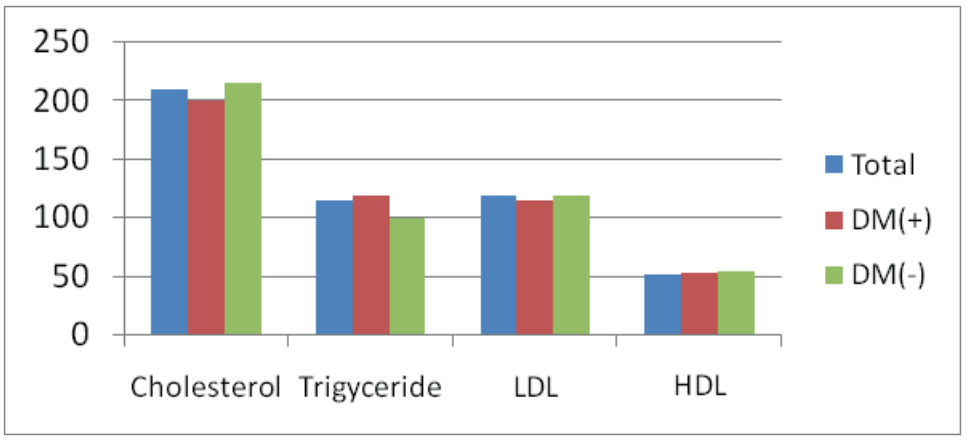

Figure 3: Shows the effect of Amlodipine on lipid metabolism after treatment there were significant differences TG between with DM(+) and DM(-) Patients.

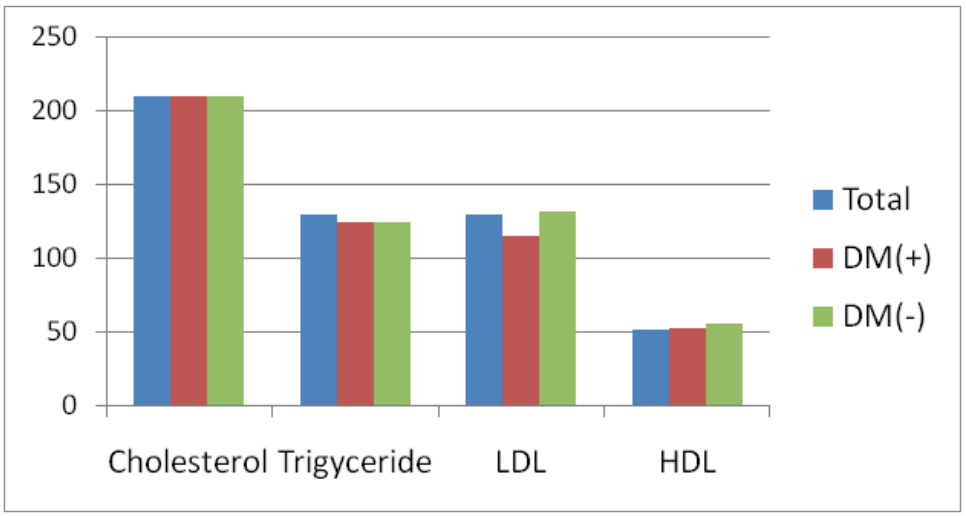

Figure 4: Shows the effect of Clinidipine on lipid metabolism after treatment there were no significant differences TG between with DM(+) and DM(-) Patients.

to reduce glomerular pressure[26]. Furthermore, regarding the effect of Cilnidipine and Amlodipine on renal function, Kojima et al, reported that the level of urinary protein elevated after Amlodipine treatment in urinary protein positive hypertensive patients as compared to baseline level, while there was no significant difference in the level of urinary protein before and after Cilnidipine treatment.[27] Fujita et al conducted a CARTER study involving patients with hypertension and chronic renal disease demonstrating that urinary protein during renin-angiotensin inhibitor therapy was further reduced by concomitant use of Cilnidipine but it was not further reduced by concomitant Amlodipine use[28]. The result from the present study were identical to those of previous reports. A possible mechanism for the renal protection effects of Cilnidipine, unlikely the other CCBs has been explained as follows. Since L type calcium channels are present primarily on afferent arterioles, the inhibition of these channels causes dilatation of only afferent arterioles, resulting in elevation of glomerular pressure. On the other hand, N- type calcium channels, which are located in sympathetic nerve endings, control both afferent and efferent arterioles, thus resulting in well-balanced dilatation of both arterioles.

Concerning lipid metabolism, neither total cholesterol, HDL-C nor LDL-C level with Amlodipine differed significantly from those with Cilnidipine in DM(+) or DM(-) groups. With Amlodipine, TG was significantly higher in DM (+) group than in DM(-) group, while no such difference was noted with Cilnidipine. These results indicate that Cilnidipine reduces TG in hypertensive patients with diabetes mellitus. The results from this study were identical to those of previous reports[29, 30].

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Conflict of interest: None declared.

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