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Original Research Article

Effect of Amlodipine and Cilnidipine on Heart Rate, Blood Pressure, Albuminuria and Lipid Profile in Stage I Hypertension in a Tertiary Care Hospital of Bihar

Kumar Mayank[1], Subhash Chandra Yadav[2], Shankar Dayal Singh[3]

[1]Tutor, Department of Pharmacology, Skmch, Muzaffarpur, Bihar, India
[2]Tutor, Department of Pharmacology, Skmch, Muzaffarpur, Bihar, India.
[3]Associate Professor, Department of Pharmacology, SKMCH, Muzaffarpur, Bihar, India.

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Corresponding author: Dr. Subhash Chandra Yadav
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Abstract

Aim: The aim of the study was to compare the clinical effectiveness of Cilnidipine and Amlodipine on blood pressure, heart rate, proteinuria and lipid profile in hypertensive patients.

Material & Methods: The present study conducted in the Department of Pharmacology, SKMCH, Muzaffarpur, Bihar, India for 4 months. Total hundred patients were included in the study. One group comprising of 50 patients took 5-10 mg Amlodipine and other group comprising of 50 patients took 10-20 mg Cilnidipine.

Results: There were no significant differences in background factors between the Amlodipine and Cilnidipine groups. Daytime, Night time and Morning 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 groups. There was significant decrease in day time and night time PR in the Cilnidipine treatment group. The protein/creatinine ratio was significantly lower with Cilnidipine than Amlodipine group. 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.

Conclusion: The study indicated that unlike Amlodipine, Cilnidipine which inhibits L-and N-type calcium channels will be useful for patients with hypertension and cardiovascular disease, diabetes mellitus or renal disease and proves to be a better alternative to existing calcium channel blockers.

Keywords: Cilnidipine, Amlodipine, Blood Pressure.

Introduction

Hypertension is a widespread public health problem and a major risk factor. [1] It may lead to damage of heart, kidney, brain, vasculature and other organs results in premature morbidity and death. [2] National and international guidelines recommend angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and beta-blockers for the management of hypertension. CCBs are among the most

used antihypertensive medications currently in the market, and the use of CCBs is especially effective for the treatment of hypertension in the elderly who frequently have large-vessel stiffness. [3] Calcium antagonists dilate blood vessels to reduce peripheral vascular resistance (PVR) which reduces blood pressure. The calcium blockers block calcium influx into vascular smooth muscle cells, resulting in vasodilatation and reduction of peripheral vascular resistance.

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] After oral administration, drug concentrations peak at 1.8 to 2.2 hours and show a half-life of 7.5 hours. It has been shown to reduce both systolic blood pressure (SBP) and diastolic blood pressure (DBP) but does not increase pulse rates (PR) or plasma catecholamines. [5] It has also been shown to inhibit the pressor response to the acute cold stress in spontaneously hypertensive rats (SHR). [6] Cilnidipine was reported to be effective in hypertensive patients with morning HTN in which sympathetic nerve over-activity was potentially involved.

Old CCB like Amlodipine and a newer CCB like Cilnidipine have shown equal efficacy in reducing blood pressure in hypertensive individuals. But Cilnidipine being an N-type and L-type calcium channel blocker is associated with a lower incidence of pedal edema compared to only the L-type channel blocked by Amlodipine. [7]

The urinary albumin, 8-hydroxy-2'-deoxyguanosine (OHdG), and liver-type fatty-acid binding protein (L-FABP) to creatinine ratios significantly decreased with Cilnidipine ($P<0.05$) compared with those with Amlodipine. [8] Thus, Cilnidipine probably exerts a greater renoprotective effect through its antioxidative properties.

De Champlain [9] showed a sustained rise in blood norepinephrine levels by more than 50% after chronic therapy of Amlodipine. The inhibitory effect on the N-type ca^{2+} channel by Cilnidipine may bestow an additional clinical advantage for the treatment of hypertension, such as suppression of reflex tachycardia. It dilates afferent and efferent arterioles in the kidney and decrease glomerular capillary pressure, thereby decreasing proteinuria and improving glomerulosclerosis. [10] Thus, the aim of the study was to compare the clinical effectiveness of Cilnidipine and Amlodipine on blood pressure, heart rate, proteinuria and lipid profile in hypertensive patients.

Material & Methods

The present study conducted in the Department of Pharmacology, SKMCH, Muzaffarpur, Bihar, India for 4 months. Total hundred patients were included in the study. One group comprising of 50 patients took 5-10 mg Amlodipine and other group comprising of 50 patients took 10-20 mg Cilnidipine.

Approval of protocol and study document was taken from institutional ethical committee before study commencement. The written informed consent patients was screen for selection criteria. Cilnidipine was administered orally at the dose of 10 mg. Amlodipine was administered orally once daily at the dose of 5mg. BP and Pulse rate was monitored during morning, daytime and night time and average value is recorded. In proteinuric patients, urinary protein content was standardized for urinary excretion of 1g creatinine. Serum concentration of total cholesterol, HDL-C, LDL-C and TG was determined by the enzymatic methods with an autoanalyzer.

All DM patients in this study was 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).

Inclusion Criteria

A. Age: >40yrs to <60yrs; BMI>18.5 to <30kg/m2 (normal and pre-obese).
B. Sex: Both sexes
C. Patients with Essential hypertension of mild to moderate cases (stage I & stage II) according to JNC7 (those SBP<180 and DBP<110).
D. Phase of microalbuminuria. (Spot urinary albumin creatine ratio ACR<300mg/gm).
E. Hypertensive patients on Amlodipine (2.5 to 10mg) & Cilnidipine (5 to 20mg) or combination with ARB (in a dose equivalent to 40mg of Telmisartan).
F. Controlled diabetic patient (HBA1c≤7).

Exclusion Criteria

A. Age: <40yrs to >60yrs ; BMI <18.5 to >29.99kg/sq. mt
B. All cases of hypertension with SBP≥180 and DBP≥110.
C. Patients of secondary hypertension or taking antihypertensive medicine other than additional ACEI/ARB.
D. Uncontrolled diabetes (HBA1c>7).
E. Serum creatinine≥1.2
F. Patient with liver disease
G. ACR>300mg/gm (Spot urine)
H. Patients on Pioglitazone
I. Patients with heart failure, heart block, aortic stenosis.
J. On NSAID for long term; corticosteroid and sex steroids.

Statistical Analysis: Values are 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.

Results

Table 1: Baseline characteristics of hypertensive patients

	Amlodipine	Cilnidipine
Male	35	32
Age (Years)	60±4.7	62±6.5
BMI (Kg/m^2)	24±3	23±2.6
Number with diabetes	15	18
Number with Proteinuria	12	14
Day time SBP (mmHg)	166±16	166±11
Day time DBP (mmHg)	98±8.6	100±10
Day time PR (bpm)	76±9.8	78±7.2
Nighttime SBP (mmHg)	144±18	146±16
Nighttime DBP (mmHg)	94±6.4	96±6
Nighttime PR (bpm)	62±7.2	64±8.4
Morning SBP (mmHg)	164±16	166±10
Morning DBP (mmHg)	96±6.6	98±8
Morning PR (bpm)	74±8.2	76±9.8

There were no significant differences in background factors between the Amlodipine and Cilnidipine groups.

Table 2: Blood pressure before and after treatment

	Amlodipine			Cilnidipine		
	Before	**After**	**P**	**Before**	**After**	**P**
Day time SBP (mmHg)	166±16	152±11	<0.001	166±11	154±11	<0.001
Day time DBP (mmHg)	98±8.6	90±7.8	<0.001	100±10	92±6.8	<0.001
Nighttime SBP (mmHg)	144±18	132±13	<0.001	146±16	138±14	<0.005
Nighttime DBP (mmHg)	94±8.4	88±6	<0.001	96±10	92±8	<0.001
Morning SBP (mmHg)	164±16	150±12	<0.001	166±12	156±6	<0.005
Morning DBP (mmHg)	96±6.4	91±4.4	<0.001	98±8	94±6	<0.001

Daytime, Night time and Morning 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 groups.

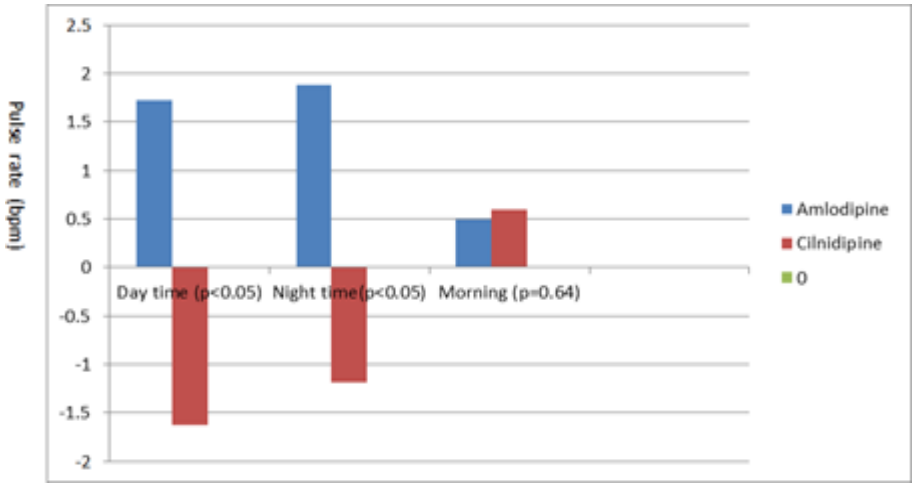

Figure 1: Change in pulse rate (PR) after Amlodipine and Cilnidipine treatment compared to the pre-treatment value by paired t-test

In the Amlodipine group, night time PR after treatment was significantly higher than that before treatment and day time PR after treatment tended to be higher than those before treatment. There was significant decrease in day time and night time PR in the Cilnidipine treatment group.

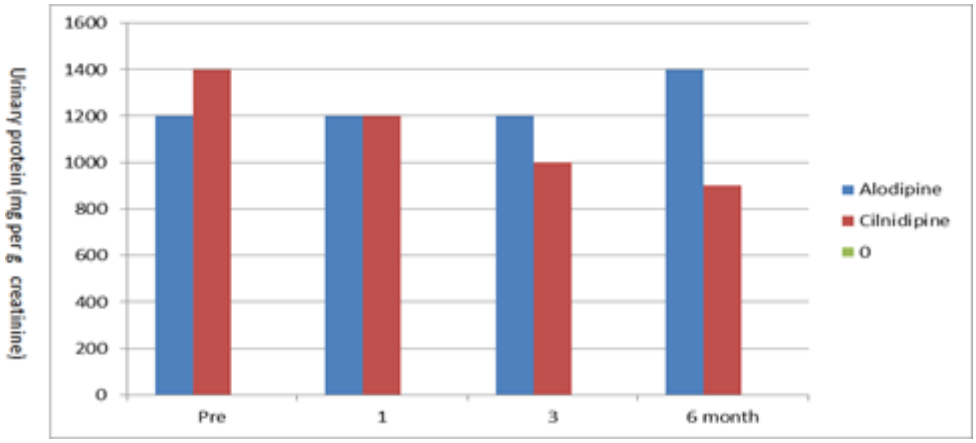

Figure 2: Change in urinary protein/creatinine ratio during the 6 month treatment period in the Amlodipine and Cilnidipine group

The protein/creatinine ratio was significantly lower with Cilnidipine than Amlodipine group.

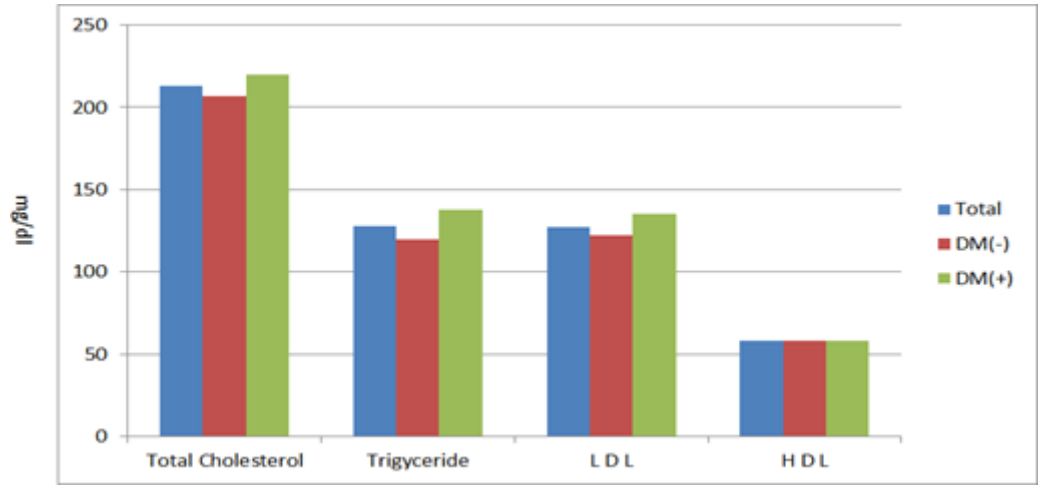

Figure 3: Effect of Amlodipine on lipid metabolism after treatment. DM(+) Patients with diabetes mellitus, DM(-) Patients without diabetes mellitus

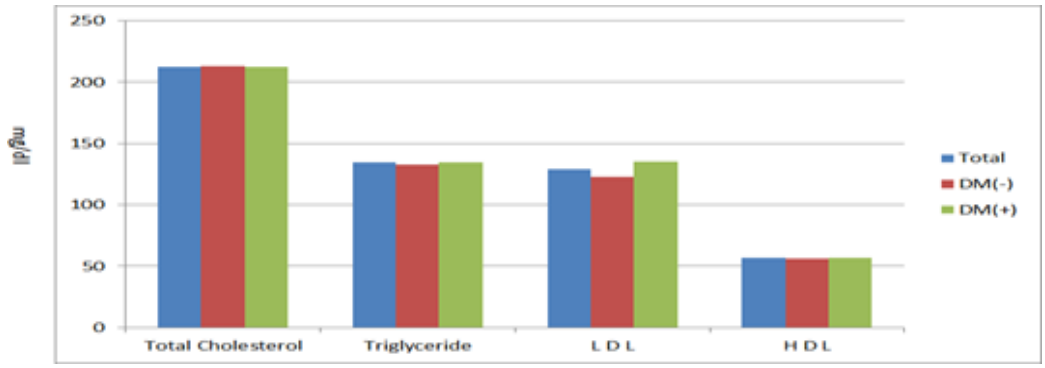

Figure 4: Effect of Cilnidipine on lipid metabolism after treatment. DM(+) Patients with diabetes mellitus, DM(-) Patients without diabetes mellitus

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(-) group.

Discussion

Hypertension (HTN) is one of the most common cardiovascular diseases, and the prevalence of hypertension continues to rise across the globe. Despite being so common, the awareness, treatment, and control of hypertension in the community are very less.[11] Calcium antagonists dilate blood vessels to reduce peripheral vascular resistance (PVR) which reduces blood pressure. The calcium blockers block calcium influx into vascular smooth muscle cells, resulting in vasodilatation and reduction of peripheral vascular resistance.[12] 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.[13] 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.[14] Previous reports indicates beneficial effect of Cilnidipine on lipid profile in addition to the antihypertensive activity.[15,16]

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. [17,18] 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 [19,20] 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. [21] It was reported that antihypertensive therapy suppressed the progression of renal dysfunction. [22] Regarding glomerular kinetics, it has been shown that inhibition of angiotensin II suppress the elevation of glomerular pressure. Among CCBs, Cilnidipine has been reported to reduce glomerular pressure.[10] 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.[23] 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. [24] 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. [25] 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.

Conclusion

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. The study indicated that unlike Amlodipine, Cilnidipine which inhibits L-and N-type calcium channels will be useful for patients with hypertension and cardiovascular disease, diabetes mellitus or renal disease and proves to be a better alternative to existing calcium channel blockers.

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