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Original Research Article

Comparison of Cilnidipine and Amlodipine Effects on Twenty Four Hours Blood Pressure Variability and Pulse Rate

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Abstract: Cardiovascular diseases are major causes of death and disability across the world. Calcium channel blockers are a heterogeneous group of drugs comprising of elements with varied properties. This study compared the effects of cilnidipine and amlodipine on ambulatory BP and pulse rate using ambulatory BP monitoring in patients with essential hypertension. Cilnidipine was administered in 50 patients orally once daily at an initial dose of 10 mg for 4 weeks. If the BP remained high (BP≥140/90 mmHg), the dose was increased to 20 mg once daily for another 4 weeks. Amlodipine were administered in other 50 patients orally once daily at an initial dose of 5 mg for 4 weeks. Dose of amlodipine was increased by 5 mg once daily when BP was not successfully controlled. All patients were studied for 12 weeks. The 24-h ambulatory BP monitoring (ABPM) was performed at 4, 8 and 12 weeks. Effects of cilnidipine and amlodipine on 24 hours blood pressure and pulse rate. 24 hours systolic and diastolic blood pressures were controlled in both groups without any statistically difference. But in amlodipine group, 24 hours pulse rate was significantly higher than cilnidipine group. Higher heart rate is associated with a long term risk of cardiovascular mortality. Therefore antihypertensive drugs that do not increase the heart rate are preferable. Thus cilnidipine is beneficial drug for hypertension treatment as this does not cause reflex tachycardia.
Keywords: Cilnidipine, Amlodipine, Hypertension

INTRODUCTION

Cardiovascular diseases are major causes of death and disability across the world. According to the Global Burden of Disease study report, in 1990, around 5.2 million deaths in economically developed and 9.1 million deaths in developing countries occurred due to cardiovascular diseases [1]. Achieving blood pressure goals is pivotal in reducing cardiovascular mortality and morbidity associated with hypertension. Associated cardiovascular complications and end-organ damage can be reduced significantly by even achieving small reductions in BP. In India, HTN is primarily accountable for almost 57% of all deaths due to stroke and 24% of all deaths due to coronary artery diseases. Hypertension is a controllable disease. By decreasing blood pressure by 2 mmHg, almost 1,51,000 and 1,53,000 deaths due to stroke and coronary artery disease, respectively, can be prevented in India [2].

Calcium channel blockers (CCBs) are a heterogeneous group of drugs comprising of elements with varied properties. They are grouped into two types: dihydropyridines and non-dihydropyridines. They block L-type calcium channels which do not allow the calcium influx across membranes. The difference between dihydropyridines and non-dihydropyridines is that while the former binds to L-type calcium channels in vascular smooth muscle, resulting in vasodilation, the latter binds to L-type calcium channels in the myocardium at the SA and AV nodes, resulting in lowering the heart rate. Dihydropyridines causes a baroreceptor mediated reflex tachycardia and non-dihydropyridines causes slower atrioventricular nodal conduction.

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Cilnidipine a unique Ca2+ channel blocker because of its inhibitory action on the sympathetic N-type Ca2+ channels along with L-type Ca2+ channels [3]. Cilnidipine has been classified as a fourth-generation CCB based on its actions on sympathetic neurotransmitter release.7 Cardioprotective, renoprotective and neuroprotective effects of cilnidipine have been reported in clinical or animal studies. N-type calcium channels regulate sympathetic nerve activity, and aberrant sympathetic nerve stimulation is a major cause of hypertension [4, 5]. Cilnidipine is thus a useful antihypertensive drug that may not cause an excessive decrease in BP or a reflex tachycardia [6, 7]. Both cilnidipine and amlodipine have clinical benefits resulting from the unique characteristics of each agent. This study compared the effects of cilnidipine and amlodipine on ambulatory BP and pulse rate using ambulatory BP monitoring in patients with essential hypertension.

MATERIALS & METHODS

Study Design: This is an observational study. Study Setup: This study is conducted at Department of General Medicine of a tertiary care centre. Study Duration: The duration of study was two years; November-2014 to October-2016.Sampling: Simple randomized sampling technique is used for selection of desired samples according to inclusion criterion. Sample Size: 100 adult patients (age >18 years) of essential hypertension were evaluated for possible inclusion in this study. Inclusion criteria: All adults who had blood pressure > 140/90 mmHg on two separate occasions or already on treatment for hypertension were included in this study.Exclusion criteria: The exclusion criteria were patients of secondary hypertension, history of alcohol ingestion (> 30 gm/day for men and > 20 gm/day for women), coronary artery disease, cerebrovascular accidents, congestive heart failure, or malignancy.

METHODS

Demographic characters like age, sex, height, waist circumference and weight of all subjects were noted. Detail history was recorded, general physical examination was done and detailed systemic examination was done. Routine investigations including complete blood counts, peripheral smear examination, fasting blood glucose (FBG), 2-hr postprandial blood glucose (PPBG), HbA1c, kidney function tests, liver function tests and Lipid profile were done. Cilnidipine was administered in 50 patients orally once daily at an initial dose of 10 mg for 4 weeks. If the BP remained high (BP≥140/90 mmHg), the dose was increased to 20 mg once daily for another 4 weeks. Amlodipine were administered in other 50 patients orally once daily at an initial dose of 5 mg for 4 weeks. Dose of amlodipine was increased by 5 mg once daily when BP was not successfully controlled. All patients were studied for 12 weeks. The 24-h ambulatory BP monitoring (ABPM) was performed at 4, 8 and 12 weeks.

Ethical Consideration: Prior to conduct of the present study, the protocol of the study was submitted to ethical and scientific committee of hospital. After getting due approval from these two committees, the present study was initiated. Also prior to conduct of study related procedure / investigation, a voluntary written informed consent was taken from the patient /legally acceptable representative.Statistical Technique: Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. The qualitative data were expressed in percentages and quantitative data were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables.

RESULTS

Table 1 shows the demographic characteristics of all 100 hypertensive subjects. Baseline characteristics of both groups were comparable. ($p>0.05$) Baseline serum creatinine, SGPT, hemoglobin and fasting blood sugar were normal in both groups. ECG of all subjects did not show signs of myocardial ischemia.Table 2 shows the effects of cilnidipine and amlodipine on 24 hours blood pressure and pulse rate. 24 hours systolic and diastolic blood pressures were controlled in both groups without any statistically difference. But in amlodipine group, 24 hours pulse rate was significantly higher than cilnidipine group.

Table−1: Demographic characteristics of Cilnidipine and Amlodipine Group (Before treatment)

Characteristics	Cilnidipine group (n=50)	Amlodipine group (n=50)	P value
Clinic SBP (mmHg)	168.2±8.5 mmHg	172.4±7.3 mmHg	p>0.05
Clinic DBP (mmHg)	96.2±6.5 mmHg	95.5±4.5 mmHg	p>0.05
Clinic PR (bpm)	74±6	78±6	p>0.05
BMI (kg/m^2)	26.3±3.5	25.9±4.4	p>0.05
Serum Creatinine (mg/dl)	0.9±0.4	1.0±0.4	p>0.05
Hemoglobin (gm/dl)	11.4±1.9	12.1±2.6	p>0.05
FBS (mg/dl)	83.4±6.4	84.3±5.9	p>0.05
24 hours SBP	158.2±9.5 mmHg	152.4±8.3 mmHg	p>0.05
24 hours DBP	88.2±5.5 mmHg	89.5±4.3 mmHg	p>0.05
24 hours PR	73±5.4	76±3.8	p>0.05

Table−2: Blood pressure and Pulse rate after Cilnidipine and Amlodipine treatment

Characteristics	Cilnidipine group (n=50)	Amlodipine group (n=50)	P value
24 hours SBP	118.2±8.5 mmHg	120.4±7.3 mmHg	p>0.05
24 hours DBP	68.2±7.5 mmHg	69.5±7.3 mmHg	p>0.05
24 hours PR	70±4.4	86±8.8	P<0.005

DISCUSSION

In our study, amlodipine and cilnidipine both caused reduction in blood pressure but 24 hours pulse rate was higher in patients who were treated with amlodipine. In a study by Tominaga M *et al*, Cilnidipine was given to 14 hospitalized patients with essential hypertension, and 24-hour ambulatory blood pressure (BP) monitoring was performed. Once-daily administration of cilnidipine (5-20 mg) for 1-3 weeks decreased the 24-hour average BP significantly from 149 +/- 4/88 +/- 2 mmHg to 141 +/- 3/82 +/- 2 mmHg without any change in the pulse rate. The decrease in ambulatory BP by cilnidipine was evident during the daytime (156 +/- 4/93 +/- 2 mmHg to 143 +/- 5/84 +/- 2 mmHg, $p < 0.01$ for systolic BP and $p < 0.01$ for diastolic BP), while it was mild during nighttime (141 +/- 4/80 +/- 2 mmHg to 133 +/- 4/76 +/- 3 mmHg, $p < 0.05$ for systolic and ns for diastolic BP). The decrease in the ambulatory BP over the whole day and during the nighttime was significantly correlated with the basal ambulatory BP levels. When the subjects were divided into the high ambulatory BP (n = 7) and low ambulatory BP (n = 7) groups, the BP reduction by cilnidipine was evident throughout 24 hours in the high ambulatory BP group, while it was mild and significant only during daytime in the low ambulatory BP group. In summary, once-daily cilnidipine exerts a sufficient and prolonged reduction of BP without an increase in the pulse rate in patients with hypertension. The potency of cilnidipine to decrease ambulatory BP may depend on the basal ambulatory BP level. Cilnidipine is thus a useful antihypertensive drug that may not cause an excessive decrease in BP or a reflex tachycardia [8]. Junichi Minami et al also showed that Cilnidipine significantly decreased the 24 h blood pressure by 6.5 ± 1.7 mm Hg systolic (mean ± s.e.mean; $P < 0.01$) and 5.0 ± 1.1 mmHg diastolic ($P < 0.01$), whereas cilnidipine did not change heart rate or any indices of power spectral components [9]. Cilnidipine is a unique dihydropyridine derivative L-type Ca^{2a+} channel blocker with an inhibitory action on the sympathetic N-type Ca^{2a+} channels. Depolarization of the membranes of the vascular cells or sympathetic neurons, results in contraction of the vascular smooth muscles or release of neurotransmitters. In anti-hypertensive therapy with L-type Ca^{2a+} channel blockers like nifedipine and amlodipine, hypotension lead to the sympathetic reflex which activates the sympathetic N-type Ca^{2a+} channels. This results in several cardiovascular responses such as tachycardia, vascular contraction and renin secretion. The N-type Ca^{2a+} channel blocking property of cilnidipine allows it to directly inhibit the release of sympathetic neurotransmitter, which reduces the risk of cardiovascular diseases closely associated with activation of sympathetic nerve [10].

CONCLUSION

Higher heart rate is associated with a long term risk of cardiovascular mortality. Therefore antihypertensive drugs that do not increase the heart rate are preferable. Thus cilnidipine is beneficial drug for hypertension treatment as this does not cause reflex tachycardia.

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