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Research Article

EVALUATION OF RENOPROTECTIVE EFFECT OF CILNIDIPINE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION AND TYPE 2 DIABETES MELLITUS – A PROSPECTIVE STUDY

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ABSTRACT

Objective: The objective of the study was to evaluate the renoprotective effect of cilnidipine by estimating urinary albumin and creatinine levels in mild-to-moderate hypertension (HTN) with type 2 diabetes mellitus (DM) and also evaluate the adverse drug profile of cilnidipine in the same patients.

Methods: This was a single-center, prospective, open-labeled, randomized study. A total of 60 patients of either gender aged between 30 and 60 with mild-to-moderate HTN with type 2 DM were included in the study. Urine albumin and urine creatinine were measured at day 1 and day 181. Blood pressure (BP) was measured in all visits. The drug cilnidipine at a dose of 10–20 mg oral was given and the corresponding improvement in the levels of urine albumin and other parameters was identified.

Results: There was a significant reduction in the mean systolic BP from 150.07±5.44 mmHg in visit 0 to 123.03±5.23 mmHg in visit 3. And also, there was a significant reduction in the mean diastolic BP from 95.5±8.15 mmHg in visit 0 to 80.8±2.42 mmHg in visit 3. The mean heart rate at visit zero was 76.71±4.86. At the end of 6 months of treatment, there was a significant reduction to 70.63±2.74. There was a significant reduction in the microalbuminuria from 66.62±8.39 to 38.8±6.45. The mean reduction was 27.56±10.25. There was no change in the creatinine level.

Conclusion: The study reveals that the drug cilnidipine is safe and effective in reducing the microalbuminuria and also effectively reduces BP in hypertensive patients. Hence, the drug cilnidipine can be safely administered to the patient with diabetes and HTN.

Keywords: Cilnidipine, Renoprotective, Microalbuminuria, Hypertension, Diabetes mellitus.

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INTRODUCTION

Hypertension (HTN) and diabetes mellitus (DM) are a worldwide major public health problem and a major risk factor for renal failure and other organ damage. In a prospective cohort study, the development of type II diabetes was almost 2.5 times as likely in persons with HTN than in normotensive patients [1]. This is in coincidence with substantial evidence of the increased prevalence of HTN in diabetic persons [2]. The risk for cardiovascular disease (CVD) is quadruplicate higher in patients with both DM and HTN as compared to the normotensive non-diabetic controls [3,4]. Diabetic nephropathy and microalbuminuria are found to be strong predictors and vital indicators of cardiovascular and also overall morbidity and mortality in patients of diabetes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) can be used in case of albuminuria. Although ACE inhibitors and ARBs reduce proteinuria significantly and equally effective in lowering blood pressure (BP), many adverse effects are noticed with these drugs. The use of ACE inhibitors or ARBs may exacerbate hyperkalemia in patients and are contraindicate in advanced renal insufficiency. ACE inhibitors may cause a rapid decline in renal function, hence, they are contraindicated in older patients with bilateral renal artery stenosis. ARBs can cause hyperkalemia in patients with renal failure and in patients taking potassium-sparing diuretics. When the patients do not respond to ARB monotherapy, diuretics or non-dihydropyridine calcium channel blockers (CCBs) are the second line of drugs. However, diuretics can cause metabolic side effects and non-dihydropyridine CCBs can cause a negative ionotropic effect. The dihydropyridine CCB, amlodipine is a widely used drug but has no renoprotective property. Cilnidipine is a novel and unique dihydropyridine derivative CCB blocker that blocks both L-type and N-type voltage-dependent calcium channels [5]. It inhibits sympathomimetic activity in contrast to other dihydropyridines. And also, the incidence of ankle edema is low with cilnidipine when compared to amlodipine [6].

The present study was, therefore, designed and conducted to evaluate the renoprotective effect of cilnidipine by estimating urinary albumin and serum creatinine levels in hypertensive patients with concomitant type 2 DM and albuminuria.

METHODS

This was a prospective, open-labeled, randomized study conducted for 1 year in Vinayaka Missions Kirupananda Variyar Medical College and Hospital, Salem. A total of 60 patients of either gender aged between 30 and 60 with mild-to-moderate HTN and type 2 DM were included in the study.

Inclusion Criteria

Mild-to-moderate HTN patients with type 2 DM (either gender aged between 30 and 60 years) and microalbuminuria in the range of 30–300 mg/L are included in the study.

Exclusion Criteria

Hypertensive subjects with systolic BP (SBP) ≥180 mmHg and/or diastolic BP (DBP) ≥110 mmHg, subjects on two or more antihypertensive medications, pregnant and lactating women, those with severe heart failure or with severe liver dysfunction, those with end-stage renal disease, and those undergoing dialysis were excluded from the study.

After a detailed history, physical examination, clinical examination (SBP, DBP, and heart rate), and laboratory investigation (Hb, TC, DC, ESR, LFT, RFT, and ECG), the recruited patients were given cilnidipine 10–20 mg once daily ½ h after breakfast for 6 months. Patients enrolled in the study were not permitted to use any other medications apart from the antihypertensive drugs given to them. All the recruited patients completed the study.

The study protocol was approved by the Institutional Ethics Committee VMKVMC/IEC/14/8. Informed consent was obtained from the patient before conducting the study by explaining the study procedures to the patient.

Patient Monitoring

BP, heart rate, proteinuria, and serum creatine were measured in all patients. There were four visits (Visit 0 at the start of the study, Visit 1 at 1 month, visit 2 at 3 months and Visit 3 at 6 months). During each visit, the SBP, DBP, and heart rate were measured. Urine albumin and serum creatinine were measured at day 1 and 6 months. Microalbuminuria can be diagnosed from elevated concentrations in a spot sample (30–299 mg/L). Urine albumin levels were estimated by latex turbidimetry-microalbumin-turbilatex test (Euro Diagnostics). The drug cilnidipine at a dose of 10–20 mg oral was given to all patients and the corresponding improvement in the levels of urine albumin and other parameters were identified.

Statistical Analysis

All parameters such as age, body mass index (BMI), BP, heart rate, proteinuria, fasting blood sugar, postprandial blood sugar, and serum creatinine were expressed as mean±standard deviation (SD).

RESULTS

Demographic Data

In about 60 patients, there were 38 (63.33%) males and 22 (36.6%) were females. Patients between the age of 45 and 55 were selected. Mean age of the patient recruited for the study was 49.36±6.08. About 13% of the patients had the habit of smoking. These baseline demographic data are shown in Table 1.

Table 1: Baseline demographic and clinical characteristics of patients

Baseline demographic data	Mean±SD
Age (years)	49.36±6.089
Sex	38 (63.33%) males 22 (36.6%) females
Weight (Kg)	65.1±10.11
Height (cm)	162.07±6.37
BMI (Kg/m^2)	24.77±3.44
Heart rate (beats/min)	76.71±4.86
Smokers (%)	8 (13%)
Fasting blood sugar (mg/dl)	140.13±9.24
Postprandial blood sugar (mg/dl)	227.88±17.28
SBP mmHg	150.07±5.44
DBP mmHg	95.5±8.15
Albuminuria (mg/L)	66.62±8.39
HbA1C (%)	8.05±0.87
Creatinine (mg/dl)	0.88±0.11

SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Efficacy Evaluation

Table 2 shows that there was a significant reduction in the mean SBP from 150.07±5.44 mmHg in visit 0 to 123.03±5.23 mmHg in visit 3 (after 6 months of treatment). And also, there was a significant reduction in the mean DBP from 5.5±8.15 mmHg in visit 0 to 80.8±2.42 mmHg in visit 3 (after 6 months of treatment). There was a significant reduction in both systolic and DBP in the first, second, and third visits. The mean heart rate at visit zero was 76.71±4.86. At the end of 6 months of treatment, there was a significant reduction to 70.63±2.74. There was a significant reduction in the microalbuminuria from 66.62±8.39 to 38.8±6.45. The mean reduction was 27.56±10.25. There was no change in the creatinine level.

Safety Evaluation

Table 3 demonstrates the adverse effects suffered by patients with cilnidipine. The common adverse effects seen with cilnidipine were headache, nausea, and fatigue. None of the patients had ankle edema.

DISCUSSION

Cilnidipine was extensively studied by researchers in its preclinical and clinical developmental stages and is still being studied. It was proved to have a reno, neuro, and cardioprotective effect – decrease in heart rate, apart from its BP lowering effect. Hence, a study was conducted to evaluate the renoprotective effect of cilnidipine in patients with mild-to-moderate HTN and type 2 DM. This study revealed that microalbuminuria was significantly reduced with cilnidipine administration and there was no serious adverse effect with cilnidipine which was reported. The study also confirmed that the cilnidipine is safe and effective in reducing microalbuminuria in hypertensive patients.

A study by Xu *et al*. [7] has shown that cilnidipine was well tolerated by hypertensive patients with a very minimal adverse event such as headache, dizziness, cough, and gastrointestinal disturbances which are comparable to amlodipine [8]. Hence, CCBs with action on N-type calcium channel can cause dilation of venules through the sympathetic system and can reduce the incidence of pedal edema compared to CCBs that act only on L-type calcium channels. Even in our study, the patients had minimal adverse effects and no patients experienced pedal edema.

Kojima *et al*. [8] and Tsuchihashi *et al*. [9] studied the renoprotective effect of cilnidipine and found outstanding results. They reported that cilnidipine had a better renoprotective effect when compared to pure L-type CCBs. It reduces glomerular filtration pressure, suppresses renin-angiotensin-aldosterone secretion, and reduces the incidence of proteinuria.

In the study by Tanaka [10], cilnidipine had a renoprotective effect compared with other CCB and concluded that heart rate and albuminuria were decreased following a switch from other CCB to cilnidipine without any change in BP. In the present study, there is a significant reduction in albuminuria with cilnidipine. However, the present study was not a comparative study.

Arijit *et al*. [11] compared the effectiveness of amlodipine and cilnidipine in patients with essential HTN and their effect on heart rate and serum uric acid levels. The study results showed that the patient had a significant reduction in heart rate and serum uric acid levels from baseline. Sarkar *et al*. [11] compared the effect of CCBs amlodipine

Table 2: Effect of cilnidipine on BP, heart rate, albuminuria, and serum creatinine

Parameters	Visit 0	Visit1	Visit 2	Visit 3
SBP (mmHg)	150.07±5.44	138.47±6.86	128.9±5.95	123.03±5.23
DBP (mmHg)	95.5±8.15	87.77±4.73	83.27±3.90	80.8±2.42
Heart rate (Beats per min)	76.71±4.86	75±3.98	73.1±3.176	70.63±2.74
Albuminuria (mg/L)	66.62±8.39	–	–	38.8±6.45
Creatinine (mg/dl)	0.88±0.11	–	–	0.89± 0.11

BP: Blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 3: Data related to adverse effects

Adverse effect	No (%)
No ADR	40
Headache	6
Fatigue	4
Nausea	3
Vomiting	1
Abdominal pain	2
Fatigue+nausea	3
Headache+nausea	1
Total	60

ADR: Adverse drug reaction

and cilnidipine and found that the elevation of creatinine was more suppressed by the cilnidipine than amlodipine. The study concluded that cilnidipine has better renoprotective profile than amlodipine. This is comparable with our study that showed no change in creatinine level.

Soeki *et al.* [12] compared the antioxidant and antiproteinuric effects of cilnidipine and amlodipine in hypertensive patients. The study suggested that cilnidipine has a greater antiproteinuric effect than the amlodipine when used in combination with renin-angiotensin system inhibitor.

In a study conducted by Singh *et al.* [13], there was a greater reduction in microalbuminuria by both enalapril and cilnidipine together than enalapril alone. Our study, Shajahan *et al.* [14] showed that there was a significant reduction in heart rate for patients treated with cilnidipine. Furthermore, there was a significant reduction in both systolic and DBP. Adverse events were less, and tolerability was better with cilnidipine.

Albuminuria is an independent risk for cardiovascular events. It was already reported that an increase in albuminuria elevates the risk of developing CVD and death. Reducing albuminuria through treatment reduces the risk. Even with highest normal level of albuminuria, the risk for cardiovascular events is increased. From the study, it is well understood that cilnidipine can reduce BP, elevated creatinine levels, heart rate, and microalbuminuria. Hence, cilnidipine is considered to have a renoprotective effect.

Limitations of the Study

The main drawback of our study was that it was not a comparative study. The other limitations are single-centered, open-labeled study with a small number of patients. Hence, an attempt should be made to extend the study with a large number of patients in multicenter with comparative groups.

CONCLUSION

From this study, we can conclude that cilnidipine can significantly reduce BP and microalbuminuria in mild-to-moderate hypertensive patients with DM. Hence, it can be used in renal compromised patients.

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AUTHORS' CONTRIBUTIONS

All authors have contributed equally to bring this original article effectively.

CONFLICTS OF INTEREST

The authors had no conflicts of interest to declare in relation to this article.

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