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Study on the antiproteinuric efficacy of Cilnidipine as an add on therapy to Ramipril in patients of Diabetic Nephropathy

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Abstract

Background: Diabetic Nephropathy can be attributed to uncontrolled Diabetes Mellitus. A clinical marker indicating renal dysfunction is proteinuria. The first choice in the management of proteinuria is Angiotensin Receptor Blockers (ARB) or Angiotensin Converting Enzyme-Inhibitors (ACE-I). However, they may fail to halt the progression of proteinuria even at their maximum dose. Previous studies have indicated that the antiproteinuric efficacy of ACE-Is can be enhanced by the addition of Calcium Channel Blockers (CCB).

A dual L/N-type CCB, Cilnidipine decreases the intraglomerular pressure by dilating the glomerular efferent and afferent arterioles resulting in an antiproteinuric effect. This study assessed the antiproteinuric efficacy of Cilnidipine after being added to Ramipril in diabetic nephropathy.

Methods: The following interventional study was conducted over a one-year duration and included 60 patients with Stage-2 to Stage-4 Diabetic Nephropathy. The values of serum creatinine, urine protein, urine creatinine and urine protein creatinine ratio (UPCR), were recorded at baseline and at 12 weeks, after Cilnidipine (10-20 mg/day) was added to the existing treatment with Ramipril (2.5-20mg/day). The primary end point was a decrease in the level of UPCR.

Results: At 12 weeks there was a significant decrease in the levels of serum creatinine from 1.44±0.41 to

1.28±0.43 mg/dl ($p<0.05$). There was also a significant reduction observed in the value of UPCR from 3.3±1.19 to 3.1±1.05 ($p<0.05$).

Conclusions: The following study observed that the addition of Cilnidipine to Ramipril in Diabetic Nephropathy decreased the presence of proteinuria, indicating its efficacy in halting the progression of diabetic kidney disease.

Keywords: Angiotensin converting enzyme inhibitors, Calcium channel blockers, proteinuria, Diabetic Nephropathy

Introduction

Diabetes is one of the most common non- communicable diseases. Globally it is certain to be the most challenging health care problem of the 21st century. The Indian council of medical research has predicted that by the year 2030 India's diabetes burden will be almost 87 million [1]. Complications of diabetes have resulted in an increased disability and reduced life expectancy. Diabetes affects many organ systems and causes complications such as coronary artery disease, peripheral artery disease, stroke, retinopathy, and renal failure. Amongst all these complications patients with diabetes are 17 times more prone to develop diabetic kidney disease which is the most common cause of end stage renal disease (ESRD) [2].

Diabetic kidney disease is characterized by morphological and ultrastructural changes in the kidney including expansion of the molecular matrix, loss of the charge barrier on the glomerular basement membrane and an increase in the intraglomerular pressure leading to increased permeability to proteins [3]. Clinical proteinuria which is the excretion of protein in urine is a well-established marker of renal dysfunction and reliably predicts it even before reduction in the estimated glomerular filtration rate (eGFR). The course of kidney disease in diabetes starts with micro albuminuria (30-300 mg/ day), then macroalbuminuria (more than 300mg/day) evolving to azotaemia which finally culminates to ESRD. Therefore, an early diagnosis and an appropriate management can predict and prevent the impending renal dysfunction [4]. Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) have shown reno protective effects in patients of diabetic kidney disease. These drugs reduce proteinuria, delay its progression, postpone renal insufficiency, and improve survival and are hence known to be the first line agents for treatment. However, even at the maximum tolerated dose these agents may not be able to achieve target reduction in proteinuria. Thus, it is obligatory for newer treatment regimens to be introduced to treat this crippling disease.

One of these regimes involve agents like the Calcium Channel Blockers (CCBs). Conventionally L-type CCB Amlodipine has been used for controlling the progression of proteinuria. However, some studies have considered its reno protective effects to be unsubstantial [5]. Therefore, recently introduced dual L/N-type CCB, Cilnidipine has emerged as a potential alternative to L-type blocking CCBs. Cilnidipine blocks the N-type calcium channels in addition to the L-type channels, located in the glomerulus of kidneys, bringing about dilation of not only the afferent arterioles but also the efferent arterioles, leading to a decrease in the intraglomerular pressure, hence bringing about its antiproteinuric effect. This function cannot be achieved by using Amlodipine [5]. Hence, the present study was aimed to study the antiproteinuric effects of Calcium channel blocker Cilnidipine as an add on therapy to Ramipril in patients of diabetic kidney disease.

Materials and methods

This interventional study was conducted by the department of Pharmacology in collaboration with the department of medicine, HIMS, Dehradun over a period of 12 months after clearance granted by institutional ethics committee.

A total of 60 patients attending the medicine OPD diagnosed with diabetic nephropathy with uncontrolled proteinuria were included in the study for 12 weeks, after taking prior written informed consent. The study included patients of diabetic kidney disease who satisfied all of the following requirements:(1) Men or women more than 18yrs of age;(2) Patients diagnosed with diabetic nephropathy (Stage-2 to Stage- 4); Patients with proteinuria (>200mg/dl) even at maximum tolerated dose of Ramipril (2.5-20mg/day) for 6 months;(3) HBA1 c≥ 6.5%;(4) estimated glomerular filtration rate (eGFR) 15-90 ml/min/1.73m^2;(5) Patients with serum creatinine levels ≤3mg/dl. The exclusion criteria included (1) Patients above 75yrs of age;(2) Hypertensive emergencies;(3) Stroke within 3 months of start of study;(4) Patients with Chronic Liver disease;(7) Pregnant and lactating females;(8) History of severe side effects of CCBs or ACE inhibitors. The patients eligible for the study in addition to Ramipril were started on Cilnidipine (5-20mg/day). A follow up after a period of 12 weeks was done and blood pressure, urine protein creatinine ratio (UPCR), serum creatinine was measured and antiproteinuric efficacy was assessed. The primary end point was change in the UPCR from the pre-treatment period to 12 weeks. The secondary end points included reduction in the serum creatinine, UPCR level and an increase in the value of eGFR, indicating improvement in kidney function. In addition to this all adverse drug reactions during the study were recorded.

The statistical analysis was based on standard descriptive statistical tests using the IBM SPSS version 20 software. Demographic data such as age and duration of disease is represented as mean ± SD. The Intragroup comparison of serum creatinine, urine protein, urine creatine, UPCR and eGFR was done using the paired students T-test. The p value of <0.05 was considered statistically significant.

Results

This study was performed to access the antiproteinuric efficacy of Cilnidipine an L/N type CCB as an add on therapy to ACE-I Ramipril in patients of Diabetic kidney disease. A total of 60 patients attending the medicine OPD of Himalayan Institute of Medical sciences were included in the study. The age of the patients ranged from 50-75 years with a mean duration of diabetes mellitus for 13.53±4.57 years. The BMI of the patients was in the normal range 23.7±2.42kg/m^2 and most of the subjects in the study were non-alcoholics and non-smokers (Table1).

There was a positive correlation observed between the duration of diabetes mellitus and an increase in the level of proteinuria (Figure 1).

In the study it was also observed that there was an increase in the eGFR which was statistically significant at p<0.05 (Table 2). Moreover, the serum creatinine levels showed a significant decrease at 12 weeks at p <0.05 (Table 2). There was also a strikingly significant reduction in the level of urine protein which in turn resulted in a significantly reduced UPCR level from baseline at 12 weeks after addition of Cilnidipine (Table 3).

The adverse events that were observed during the study were nausea and vomiting followed by pedal edema and

palpitation. There was no complain of brassy cough, urticaria or angioedema that was reported (Table 4).

Discussion

In the following study the anti-protein uric efficacy of Cilnidipine was assessed as an add on therapy to Ramipril in diabetic kidney disease patients. The mean duration of diabetes mellitus of the subjects enrolled in the study was 13.53±4.57 years this was similar to another study by Kishan et al in which the mean duration of diabetes mellitus of the subjects enrolled was 12.6±4.2 years [6]. This duration is relevant to the fact that Diabetic nephropathy is a devastating microvascular complication which may begin if diabetes is poorly controlled or inappropriately managed. It can begin as early as 5 years after the onset of diabetes mellitus and result in end stage renal disease (ESRD) after a period of 5-10 years.

Moreover, in the present study the baseline values of serum creatinine were 1.44±0.41 mg/dl which after addition of Cilnidipine reduced to 1.28±0.43 mg/dl. This finding contrasted with the study conducted by Fukumoto et al in which there was no significant reduction in the serum creatinine levels even when Amlodipine was replaced by Cilnidipine as an add on to ACE-I for a period of 6 months [7]. The mean eGFR of the patients also increased after addition of Cilnidipine, this observation was in accordance with the study done by Abe M et al and Konoshita T et al. in which there was an increase in the eGFR value [8,9].

Furthermore, there was also a significant reduction in the UPCR levels, this reduction was in accordance with a study done by Fujita et al which demonstrated a similar effect after addition of Cilnidipine to ACE-Is [10]. The reason of this decreased UPCR levels is the property of Cilnidipine being a dual L/N type calcium channel blocker that dilates the efferent as well as the efferent arterioles reducing the glomerular pressure and decreasing proteinuria in diabetic nephropathy preventing its progression [11].

The major limitation of this study was a small sample size and short duration of follow up. Therefore, it is recommended that further prospective studies with larger sample size and longer follow up are conducted such that the clinical significance of the use of Cilnidipine in Diabetic Nephropathy can be strengthened, especially in the Indian population.

Conclusion

The initial choice preferred for the treatment of proteinuria is ACE-I or ARBs, but even at a dose which is maximally tolerated, they may not be able to cease the progression of proteinuria. This has now resulted in an upcoming change in trend of adding a CCB to the already prescribed ACE-I in a patient with Diabetic nephropathy, which may help in augmenting the antiproteinuric effect of ACE-Is. The present study demonstrates the fact that Cilnidipine if added to ramipril in patients of Diabetic kidney disease was efficacious in reducing the levels of urine protein and urine creatinine in turn reducing the UPCR value and preventing the progression of Diabetic nephropathy. Cilnidipine was also found to be relatively safe without causing any serious side effects.

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Legend Tables and Figure

Table 1: Sociodemographic profile and clinical characteristics of Diabetic Kidney Disease patients (N=60)

Sociodemographic and Clinical characteristics	Subjects (N=60)
Sex (Male/Female)	38/22
Age (years)	62.47 ± 11.13
Weight (kg)	69.22 ± 8.20

Height (m)	1.70 ± 0.05
Body Mass Index (kg/m^2)	23.7±2.42
Systolic blood pressure (mmHg)	149.85 ± 21.87
Diastolic blood pressure (mmHg)	83.1 ± 12.1
Duration of diabetes mellitus (years)	13.53 ± 4.57
Fasting Plasma Glucose (FPG) (mg/dl) at base line	135.23±5.21
HBA1c (%)	7.64 ± 1.4
Smoker: Non-Smoker	12:48
Alcoholic: Non-Alcoholic	14:46

Values are expressed in frequency & Mean ± SD.

Table 2**:** Changes in renal functions of patients with Diabetic nephropathy (N=60)

Renal Functions	At Baseline	At 12 weeks	Mean Change
Serum creatinine (mg/dl) *	1.44 ± 0.41	1.28 ± 0.43	0.16±0.21
eGFR (ml/min/ 1.73m^2) *	65.66 ± 2.76	67.25 ± 2.12	-1.5± 0.55
Serum potassium (mmol/l) *	4.7 ± 0.62	4.6 ± 0.64	0.05±0.21

Values are expressed in frequency & Mean ± SD. Paired t-test was used for analysis *p significant is <0.05

Table 3**:** Changes in protein creatinine ratio in urine of Diabetic kidney disease patients (N=60).

	At Baseline	At 12 weeks	Mean change
Urine protein (mg/ dl) *	368.05± 98.7	360.26± 97.94	7.78± 6.8
Urine creatinine (mg/dl) *	116.83± 34.7	121.68± 34.59	-4.85± 2.87
Urine protein creatinine ratio*	3.3 ± 1.19	3.1± 1.05	0.18± 0.28

Values are expressed in frequency & Mean ± SD.

Paired t-test was used for analysis

*p significant is <0.05

Table 4**:** Adverse events reported during the study

Adverse event	**Number Of subjects(N=60)**
Brassy Cough	0
Nausea/Vomiting	4
Palpitations	1
Pedal edema	2
Urticaria	0
Angioedema	0

Figure 1**:** Corelation between the duration of Diabetes Mellitus with Urine Protein.