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Research Article

COMPARISON OF ANTI-PROTEINURIC EFFECTS OF AMLODIPINE AND CILNIDIPINE AS AN ADD-ON DRUG TO BASELINE MEDICATION IN HYPERTENSIVE CHRONIC KIDNEY DISEASE PATIENTS

JESMI JAMES[1]*, DHANYA JAYAKUMAR[2], GOMATHY SANKARAN[3]

[1]Department of Pharmacology, Mount Zion Medical College, Adoor, Pathanamthitta, Kerala, India. [2]Department of Pharmacology, Government Medical College, Kochi, Kerala, India. [3]Department of Nephrology, Government Medical College, Alappuzha, Kerala, India. *Corresponding author: Jesmi James; Email: jesmijmj@gmail.com

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ABSTRACT

Objectives: The objectives of the study were to compare the anti-proteinuric effects of amlodipine and cilnidipine in individuals with Chronic Kidney Disease (CKD) on baseline medication.

Methods: This was a prospective observational study carried out in the Department of Nephrology at Government T.D. Medical College, Alappuzha spanning a duration of 1 year from January 2016 to December 2016. The study encompassed a total of 90 hypertensive CKD patients-45 were administered amlodipine and the remaining 45 were given cilnidipine in conjunction with their existing baseline medications. The inclusion criteria consisted of hypertensive CKD patients aged between 18 and 80 years possessing a Glomerular Filtration Rate (GFR) between 30 and 60 mL/min and exhibiting blood pressure readings surpassing 140/90 mmHg despite receiving a loop diuretic (Tab. Frusemide 80 mg BD), an α-blocker (Tab. Prazosin 10 mg BD) and a β-blocker (Tab. Metoprolol 50 mg BD) for a minimum duration of one month. The key parameters that were monitored were sitting systolic and diastolic blood pressure readings and proteinuria which was evaluated by determining the Urine Protein Creatinine (UPC) ratio using untimed random urine samples. The GFR was calculated utilizing the Cockcroft-Gault formula.

Results: The number of patients who improved to stage 3A CKD from stage 3B CKD were more with cilnidipine which indicates its reno-protective action. Amlodipine was seen to have no effect on UPC ratio whereas cilnidipine decreased UPC ratio significantly.

Conclusion: Unlike amlodipine, cilnidipine exhibits marked reduction in proteinuria and improved GFR thereby preventing progression of hypertensive CKD patients to end stage renal failure.

Keywords: Hypertension, Chronic kidney disease, Cilnidipine, Amlodipine, Proteinuria.

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by the gradual deterioration of renal function over an extended period, typically lasting 3 months or more. The Kidney Disease Outcomes Quality Initiative (KDOQI), established by the National Kidney Foundation, provides a comprehensive definition of CKD. According to KDOQI, CKD is identified by either kidney damage or a reduced glomerular filtration rate (GFR) persisting at <60 mL/min/1.73 m^2 for a minimum of 3 months. This definition serves as a fundamental framework for understanding and diagnosing CKD, enabling health-care professionals to identify and manage this condition effectively [1]. World-wide prevalence of CKD is found to be 8–16%.This significant prevalence underscores the substantial impact of CKD on public health worldwide. It emphasizes the importance of continued research, early detection and effective management strategies to address this widespread health concern [2]. In India, the prevalence of CKD is reported to be within the range of 0.16–0.79% [3]. CKD is a widely recognized independent risk factor for both cardiovascular disease and the development of end-stage renal failure [4]. Factors linked to the advancement of renal disease in CKD patients encompass conditions such as diabetes mellitus, hypertension and hyperuricemia. Of these factors, hypertension stands out as the primary contributor to CKD progression. Current guidelines for the management of CKD strongly advocate for rigorous hypertension control through the use of suitable antihypertensive medications. This approach is instrumental in mitigating the impact of hypertension on CKD progression and preserving renal function [5].

CKD is divided into stages based on GFR-Stage 1: Renal damage with normal or increased GFR (>90 mL/min/1.73 m^2). Stage 2: Mild GFR decrease (60–89 mL/min/1.73 m^2). Stage 3a: Moderate GFR decrease (45–59 mL/min/1.73 m^2). Stage 3b: Further moderate GFR decrease (30–44 mL/min/1.73 m^2). Stage 4: Severe GFR decrease (15–29 mL/min/1.73 m^2). Stage 5: Renal failure (GFR <15 mL/min/1.73 m^2 or on dialysis) [6]. Research has indicated that in cases of advanced CKD accompanied by stable hypertension, the utilization of Angiotensin Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers leads to a reduced necessity for prolonged dialysis and a lowered risk of mortality [7]. In addition to unmanaged hypertension, a robust predictor of diminishing renal function is the presence of proteinuria. The quantification of proteinuria is achieved through the "spot" Urine Protein: Creatinine Ratio (UPC) or Urine Albumin: Creatinine Ratio. When UPC levels are below 0.5–1 g, a more favorable prognosis is observed while values exceeding 1 indicate a swifter decline in renal function [8]. In accordance with the eighth Joint National Commission report, Calcium Channel Blockers (CCBs) have exhibited more favourable outcomes in individuals with hypertension in terms of both effectiveness and the mitigation of cerebrovascular events when contrasted with ACEIs [9].

Cilnidipine, a CCB, exhibits a unique dual mechanism of action by effectively blocking both L and N-type calcium channels. This distinctive profile is associated with superior efficacy and a reduced incidence of adverse effects when compared to other CCBs such as amlodipine. In addition, cilnidipine is recognized for its pleiotropic effects which

extend beyond its N-type calcium channel blockade. These multifaceted actions potentially contribute to its added benefits in terms of cardio and renoprotection [10].

The underlying motivation for this research lies in the prospect that cilnidipine may offer substantial renoprotective benefits in addition to other advantageous effects when compared to amlodipine. If such an advantage is observed, it would justify its inclusion alongside baseline medication with the ultimate goal of impeding the advancement toward end-stage kidney failure. Consequently, this study was conducted to assess and compare the effectiveness of cilnidipine and amlodipine in CKD patients with a particular focus on their impact on the reduction of proteinuria and the improvement of GFR over time.

METHODS

This was a prospective observational study carried out in the Department of Nephrology, at Government T.D. Medical College, Alappuzha spanning a time period of 1 year (January 2016–December 2016). The study enrolled a total of 90 patients suffering from hypertension with CKD - 45 patients receiving cilnidipine and the rest 45 patients receiving amlodipine along with the baseline medications. Patients included in the study were individuals aged 18–80 years with CKD who had a GFR ranging from 30 to 60 mL/min and blood pressure exceeding 140/90 mmHg after a minimum of one month on a treatment regimen comprising loop diuretic (Frusemide 80 mg BD), α-blocker (Prazosin 10 mg BD) and β-blocker (Metoprolol 50 mg BD). Excluded from the study were patients who were using alternative systems of medicine, pregnant women and individuals facing hypertensive or cardio-vascular emergencies.

Approval was taken from Institutional Ethics Committee (IEC No.B6/79/2015/TDMCA dated December 02, 2015) as well as from Institutional Research Committee before commencing the study. Confidentiality was maintained throughout the study. Before participation, patients provided informed written consent. During the study, patients' sitting systolic and diastolic blood pressure measurements were taken twice under standardized conditions with a 20-min interval between measurements and the mean average was used for analysis. Patient weight was assessed using a digital platform weighing scale. Detailed patient information along with the results of spot UPC ratio, serum creatinine and blood urea were meticulously recorded in the pro forma. Proteinuria in patients was assessed using the spot UPC ratio from an untimed random urine sample. To calculate the GFR, the Cockcroft-Gault formula was employed.

Cilnidipine was administered as a 10 mg oral tablet BD while amlodipine was provided as a 5 mg tablet BD. Patients had follow-up appointments every 2 months for a period of 6 months, with blood pressure recorded at each visit. If blood pressure did not reach 140/90 mmHg, amlodipine and cilnidipine doses were increased to 10 mg BD and 20 mg BD, respectively. Data entry was carried out in Excel 2010 and analysis was performed using SPSS 18. Quantitative continuous variables were presented as Mean ± Standard Deviation. The changes in UPC ratio values before and after treatment in both groups were assessed using paired t-tests.

RESULTS AND DISCUSSION

A total of 90 hypertensive CKD patients were included in the study - 45 patients received amlodipine and the rest 45 patients received cilnidipine. The gender-wise categorization of cases according to the CKD stage is given in Table 1.

The categorization of cases before treatment and after treatment at fourth visit according to the CKD stage in both amlodipine and cilnidipine groups is depicted in Fig. 1. Of the total 78 patients in stage 3B CKD, 6 in amlodipine and 9 in cilnidipine showed improvement to stage 3A.

The mean±SD of the variables under study before and after treatment at fourth visit in both amlodipine and cilnidipine groups are given in Table 2.

The mean UPC ratio of amlodipine and cilnidipine at each visit is given in Fig. 2.

Paired t-test in the amlodipine group showed no statistical difference in mean UPC ratio whereas in the cilnidipine group it was found to be statistically significant.

The mean serum creatinine of amlodipine and cilnidipine at each visit is given in Fig. 3.

The mean serum blood urea of amlodipine and cilnidipine at each visit is given in Fig. 4.

The mean GFR of amlodipine and cilnidipine at each visit is given in Fig. 5.

Paired t-test showed that the mean serum creatinine, mean blood urea. and mean GFR were statistically reduced in both groups but cilnidipine was found to have a greater effect in reducing all than amlodipine.

In this study, more patients improved from stage 3B CKD to stage 3A CKD with cilnidipine, suggesting its renoprotective effects. Cilnidipine significantly reduced proteinuria (mean UPC ratio) after the study, while amlodipine had no impact on proteinuria. Both groups experienced a statistically significant reduction in mean serum creatinine, blood urea and GFR, but cilnidipine exhibited a greater effect in reducing all of these parameters compared to amlodipine.

In the research conducted by Fujita *et al.*, it was discerned that cilnidipine exhibited a better anti-proteinuric effect compared to amlodipine. Their study revealed that when administered alongside

Table 1: Gender-wise distribution of CKD stage

CKD stage	Male	%	Female	%	Total	%
2	0	0	1	1.1	1	1.1
3A	10	11.1	1	1.1	11	12.2
3B	51	56.7	27	30	78	86.7
Total	61	67.8	29	32.2	90	100

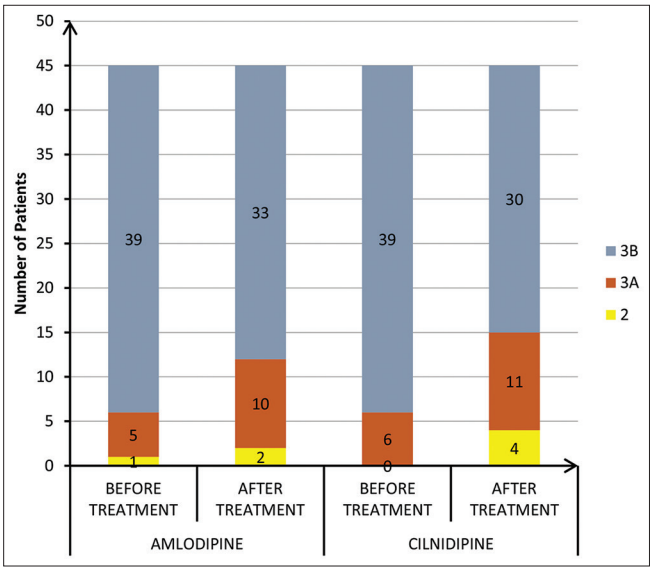

Fig. 1: CKD stage before and after treatment

Table 2: The mean±SD of the variables under study

Parameter	Amlodipine		Paired t-test (t, p)	Cilnidipine		Paired t-test (t, p)
	Before treatment	Post treatment		Before treatment	Post treatment	
UPC ratio	0.4±0.2	0.4±0.2	0.61, 0.54	0.7±0.6	0.4±0.3	5.34, <0.001
S. Creatinine	1.9±0.4	1.8±0.4	4.66, <0.001	1.9±0.2	1.5±0.15	11.03, <0.001
Blood urea	70.3±28.8	62.8±22.1	2.85, 0.007	61.9±19.8	49.9±14.3	9.26, <0.001
GFR	37.3±7.5	39.2±7.8	−4.62, <0.001	36.5±6.8	44.6±8.4	−11.23, <0.001

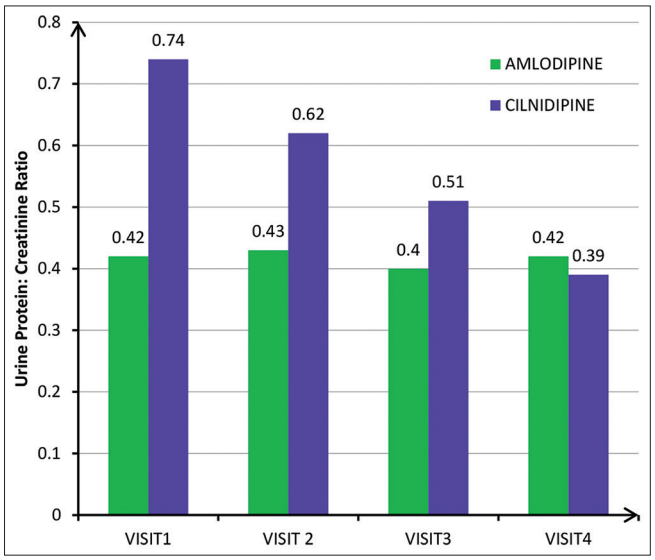

Fig. 2: Comparison of mean UPC ratio in both group

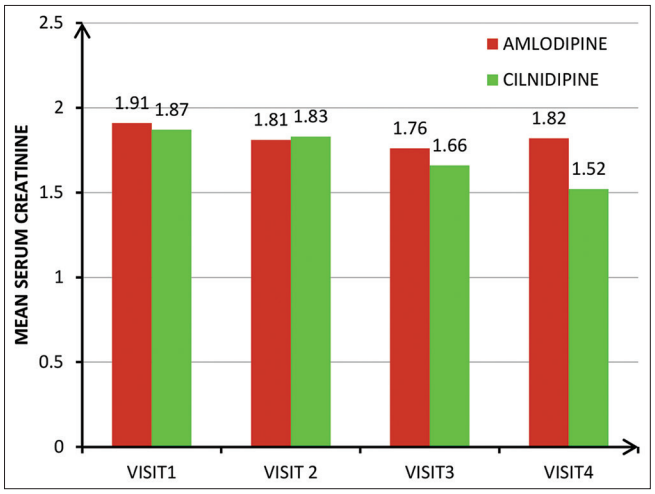

Fig. 3: Mean serum creatinine

renin-angiotensin inhibitor therapy to hypertensive patients with chronic kidney disease, cilnidipine further reduced urinary protein excretion whereas amlodipine did not produce a similar effect [11]. Notably, both groups experienced a mild increase in serum creatinine levels after 1 year of treatment, with comparable levels observed between the cilnidipine group (1.37±0.72) and the amlodipine group (1.45±0.83) [11].

Furthermore, Rose and Ikebukoro's investigation demonstrated that cilnidipine significantly diminished the excretion of urinary albumin in hypertensive patients without exerting an influence on serum creatinine concentration [12]. Kojima *et al*. and Tsuchihashi *et al*. provided evidence supporting the superior renoprotective properties of cilnidipine compared to pure L-type CCBs [13,14]. The combination

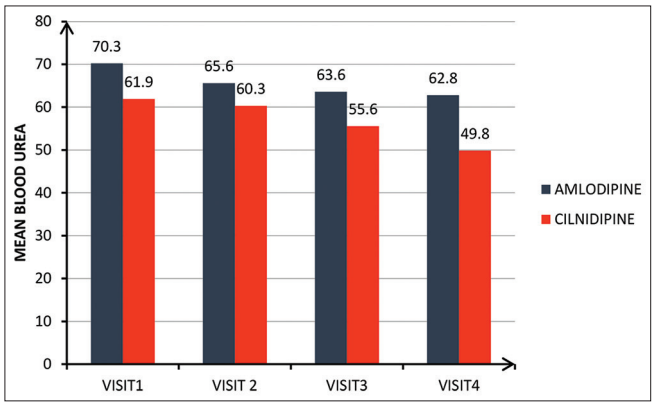

Fig. 4: Mean serum blood urea

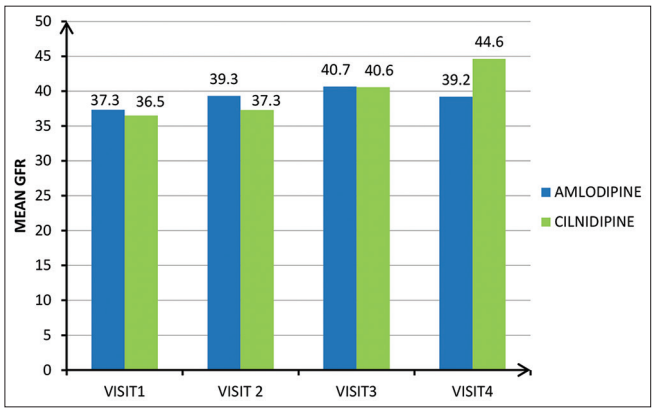

Fig. 5: Mean GFR

of cilnidipine with valsartan exhibited a more significant reduction in the albumin: creatinine ratio when compared to the use of valsartan alone [15].

Cilnidipine exerts its impact by dilating both the renal afferent and efferent arterioles, which subsequently leads to a reduction in glomerular capillary pressure. This mechanism proves instrumental in diminishing proteinuria and ameliorating glomerulosclerosis [16]. The Cilnidipine versus Amlodipine Randomized Trial for Evaluation in Renal Disease provides compelling evidence of cilnidipine's superiority over amlodipine in the context of retarding the progression of proteinuria among hypertensive patients with chronic kidney disease, particularly when combined with a renin-angiotensin system inhibitor [11].

It's worth noting that the prevalence of cardiovascular diseases and the associated mortality rates are intricately linked to renal function, illustrating the significant cardio-renal connection [4]. As such, the renoprotective actions of cilnidipine may not only address renal concerns but also contribute to cardioprotection. This dual benefit underscores the potential clinical significance of cilnidipine in managing both renal and cardiovascular aspects in patients with hypertension and chronic kidney disease.

Limitation of this study is the relatively small sample size and the short period of study. Moreover, the study was a prospective observational study. For better assessment of efficacy, a randomized controlled trial is preferable. In addition, medicines were taken by the patients in their own homes and not under direct supervision. Therefore, the complete compliance of the patients on regular intake of medication cannot be ascertained and the study relies on the assumption that the patients in the study are on regular medication.

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CONCLUSION

This study indicates that unlike amlodipine, cilnidipine exhibits marked reduction in proteinuria and improvement in GFR which proves more renoprotective action thereby preventing progression of hypertensive CKD patients to end stage kidney failure.

AUTHORS CONTRIBUTION

Jesmi James - Study conception and design, Data collection, Data Analysis and interpretation of results, Manuscript preparation. Dhanya Jayakumar - Study design guidance, Data Analysis and interpretation of results, Manuscript preparation. Gomathy Sankaran - Study conception guidance, Data collection, Interpretation of results.

CONFLICT OF INTEREST

None.

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Self.

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