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A RETROSPECTIVE STUDY ON PRESCRIBING TRENDS OF ANTIHYPERTENSIVES IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

CKD is the reduction in the GFR and urinary abnormalities or structural abnormalities of the renal tract. The aim of the study is to evaluate the prescribing trends of antihypertensives in chronic kidney disease patients. This is a retrospective observational study that was carried out in a tertiary care hospital for a period of 6 months in which data from January 2019 – January 2022 was collected from the Nephrology Department. A total of 178 cases of CKD were retrospectively analyzed, in which 107 were males and 71 were females. 129 patients had diabetes mellitus ,80 patients had coronary artery disease and 35 patients had dyslipidemia. 123 patients in this study had albuminuria and CCB was the most prescribed class of antihypertensive irrespective of all stages. There was a statistically significant difference between the prescription of antihypertensives among patients with albuminuria compared with patients without albuminuria and in the prescribing trends of diuretics, alpha blockers, β-blockers and alpha agonists in various stages of CKD. The study was done to understand about the prescribing trends of antihypertensives in CKD patients. The study concluded that CCBs were the topmost prescribed class of antihypertensive drugs in all stages of CKD and CCB+AA was the frequently prescribed combination therapy for CKD.

Keywords: Chronic kidney disease, albuminuria, GFR, prescription pattern

INTRODUCTION

CKD is defined as the reduction in the Glomerular Filtration Rate (GFR) and urinary abnormalities or structural abnormalities of the renal tract. The severity of CKD varies from 1-5 depending upon the level of GFR. CKD 1-3 is common and may not cause symptoms. It may progress to end stage renal disease but frequently remains stable for many years. CKD is an important risk factor for cardiovascular disease. As CKD becomes more advanced (stage4-5), the other body parts can also be affected. The aim of the treatment is to reverse or arrest the process responsible for CKD, to relieve symptoms and reduce cardiovascular morbidity and mortality. To prevent further renal damage, adequate control of blood pressure and reduction of proteinuria are essential. End stage renal disease (stage 5) is the point at which the patient can only sustain by dialysis or a renal transplantation **[1]**.

Hypertension is a global public health problem considered to be one of the major modifiable risk factors in developing renal and cardiovascular adverse events that result in premature disability and death with significantly rising prevalence worldwide **[2, 3]**. Hypertension is the second leading risk factor of chronic kidney disease (CKD) after diabetes **[2, 4]**. Approximately 80-85% of CKD patients were found to have hypertension and about 15.8 % of hypertensive patients were found to have CKD. The coexistence of both comorbidities results in increasing difficulties to control blood pressure **[2, 5]**. Antihypertensive medications reduce the associated complications with high blood pressure including myocardial infarction, heart failure and stroke **[6]**. Antihypertensive drugs are recommended for CKD patients in the presence and absence of hypertension for their Reno protective and cardioprotective effects. It is recommended to keep blood pressure of hypertensive patients with CKD below 130/80 mmHg **[7]**. The first-line agents being used in the treatment of hypertension among CKD patients include angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), thiazide diuretics and calcium channel blockers (CCBs). ACEIs and ARBs are the drugs of choice in the treatment of hypertension among CKD patients with albuminuria **[2, 7]**. The study intends to observe the prescribing trends of antihypertensives in chronic kidney disease patients. It also analyses the number of antihypertensive drugs based on stages of CKD, observes the utilisation of antihypertensive drugs in albuminuria and evaluate the management of hypertension in chronic kidney disease patients.

MATERIALS AND METHODS

This observational study, after obtaining ethical clearance, was conducted in a tertiary care hospital in Kerala, India from January 2019 to January 2022 with a sample size of 178. Adults in the age group above 18 years with known case of or newly diagnosed cases of chronic kidney disease who are on antihypertensive drugs were included in the study while pregnant and lactating females and patients with unreliable history were excluded.

Criteria for eligibility

Inclusion criteria

- Patients with Chronic Kidney Disease.
- Patients with hypertension (having a systolic BP > 140mm Hg and diastolic BP >90mmHg recorded in an office setting using a sphygmomanometer).
- Both dialysis and non-dialysis patients.
- Both male and female patients above 18 years.
- IP patients.
- Patients with comorbidities such as diabetes mellitus, cardiac disorders, dyslipidemia.

Exclusion criteria

- Pregnant and lactating mothers
- Pediatric patients
- Renal transplanted patients
- Patients with tumors and trauma

Brief procedure of the study:

The study was conducted in Nephrology department in a tertiary care hospital in Kerala, India. Institutional Ethics Committee approval was obtained and a retrospective analysis of medical records of CKD patients was done. A 6- month study was conducted in which around 178 patients were enrolled for the study and data collection was done between January 2018-December 2021. All relevant data including demographic details, comorbid factors, stages of CKD, blood pressure, laboratory data, details of antihypertensive drugs received by patients were recorded in the proforma. The statistical analysis was done by IBM SPSS20 (Statistical Package for Social Studies) and comparison of categorical variables were done using Chi Square test. Confidentiality of the data was maintained throughout the study.

RESULTS

1.Patient demographic characteristics

1.1 Gender

A total of 178 cases of chronic kidney disease were retrospectively analyzed, in which 107(60.1%) were males and 71(39.8%) were females.

1.2 Age

In total 178 CKD patients were included in the study, of which 72 patients were in the age group 51 -65 years and 68 patients in the age group greater than 65 years. 35 patients were in the age group 31-50 years and only

7 patients were in the age group 18 - 30 years.

1.3 Comorbidities

In total 178 CKD patients were included in the study, of which 129 patients had diabetes mellitus ,80 patients had coronary artery disease and 35 patients had dyslipidaemia.

1.4 eGFR

In total 178 CKD patients were included in the study, of which 58 patients had eGFR less than 15, 39 patients had eGFR 15-29, 35 patients had eGFR 30-59, 32 patients had eGFR 60-89 and 14 patients had eGFR greater than 90 ml/min/1.73m^2.

1.5 Albuminuria

In total 178 CKD patients were included in the study, of which 123 patients had albuminuria

1.6 Stages of CKD

In total 178 CKD patients were included in the study, of which 14 patients had stage 1, 32 patients had stage 2, 35 patients had stage 3, 39 patients had stage 4 and 58 patients had stage 5 CKD respectively.

2. Number of antihypertensives used in different stages of CKD.

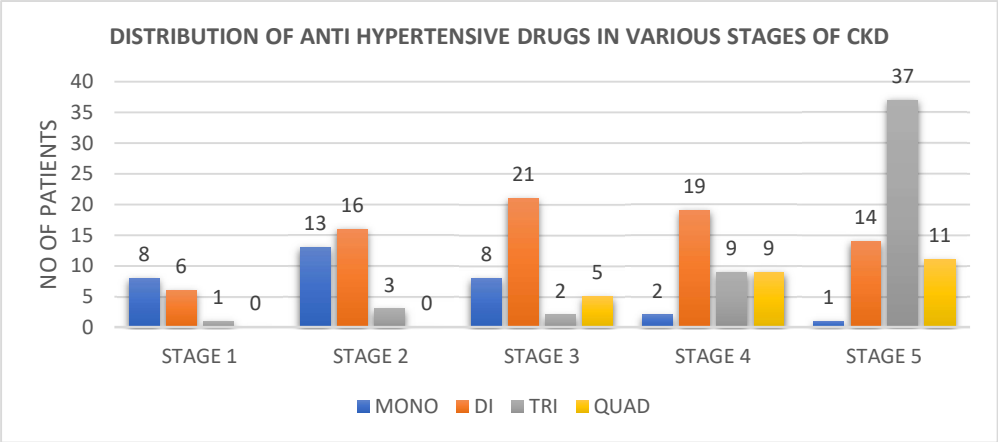

Figure 1: Distribution of antihypertensive drugs in various stages of CKD

In total there is an increase in the number of drugs prescribed with more advanced stages of CKD. Furthermore, an increase in the dual therapy has been seen in the CKD patients from Stage 1 and these is an immense increase in the triple therapy in Stage 5 CKD patients. Also, an increase has been observed in the quadruple therapy from Stage 3 to Stage 5 CKD patients.

3.Utilization of antihypertensive drugs in albuminuria

Table 1: Utilization of antihypertensive drugs in albuminuria

CLASS OF DRUGS	WITH ALBUMINURIA (%)	WITHOUT ALBUMINURIA (%)	P VALUE
CCB	105(92.9)	8(7.1)	<0.001
ACE	26(92.9)	2(7.1)	0.004
ARB	12(100)	0(0)	0.019
DIURETICS	39(97.5)	1(2.5)	<0.001
ALPHA AGONIST	43(97.7)	1(2.3)	<0.001
BETA BLOCKER	50(98)	1(2)	<0.001
ALPHA BLOCKER	28(96.6)	1(3.4)	0.001

Note. % = Percentage, P value = probability value

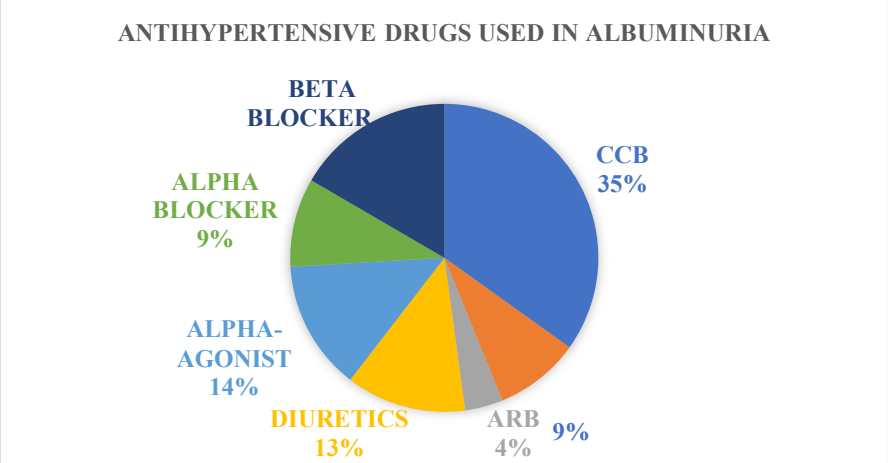

Figure 2: Utilization of Antihypertensive Drugs in Albuminuria

This is an overview of the drugs given for CKD patients with albuminuria. In this study, calcium channel blocker was the most prescribed class of antihypertensive irrespective of stages. There was a statistically significant difference between the prescription of CCBs, diuretics, ACEIs, β-blockers, ARBs, Alpha -blockers and Alpha-agonist among patients with albuminuria compared with patients without albuminuria.

3. Evaluation of management of hypertension in CKD patients

Table 2: Prescribing trends of antihypertensives in stages of CKD

STAGES (Total number of prescription)	TOP COMBINATION THERAPY IN VARIOUS STAGES (Number of prescription)	PATTERNS OF MONOTHERAPY (Number of prescription)
STAGE 5	CCB+AA+AB+BB CCB+BB+AB CCB+D	CCB BB D
STAGE 4	CCB+BB CCB+AA+D	CCB
STAGE 3	CCB+AA CCB+BB	CCB AA
STAGE 2	CCB+BB CCB+AB	CCB BB
STAGE 1	CCB+ARB	CCB

Note. % = Percentage, P value = probability value

In this study, Calcium channel blockers were the most prescribed drugs in all Stages of CKD patients. In Stage 1, ACEIs and Diuretics were the least prescribed drugs. In Stage 2, Alpha Blockers was the least prescribed. In Stage 3, the least prescribed drugs were ARB. In Stage 4 the least prescribed drugs were ACEIs and ARB. In Stage 5, the least prescribed drugs were ARB. There was a statistically significant difference in the prescribing trends of Diuretics, Alpha – blockers, Beta – blockers and Alpha- agonist in various stages of CKD.

Table 3: Prescribing Trends of Antihypertensives in Various Stages Of CKD

CLASS OF DRUGS	STAGE 1 (%)	STAGE 2 (%)	STAGE 3 (%)	STAGE 4 (%)	STAGE 5 (%)	P VALUE
CCB	9(6)	30(20.1)	28(18.8)	33(22.1)	49(32.9)	0.156
ACEI	0(0)	3(10.3)	10(34.5)	5(17.2)	11(37.9)	0.079
ARB	3(20)	2(13.3)	1(6.7)	5(33.3)	4(26.7)	0.213
DIURETIC	0(0)	5(9.3)	7(13)	20(37)	22(40.7)	<0.001
ALPHA BLOCKER	2(5.7)	1(2.9)	5(14.3)	7(20)	20(57.1)	0.006
BETA BLOCKER	5(6.8)	5(6.8)	14(19.2)	18(24.7)	31(42.5)	0.012
ALPHA AGONIST	1(1.8)	7(12.5)	9(16.1)	14(25)	25(44.6)	0.045

In this study, In Stage 1, the most frequently prescribed combination therapy was CCB+ARB and monotherapy was CCB. In Stage 2, the most prescribed combination therapies were CCB+BB and CCB+AB and the most prescribed monotherapy was CCB and BB. In Stage 3, the most frequently prescribed combination therapies were CCB+AA and CCB+BB. Also, the most prescribed monotherapy was CCB and AA. In Stage 4, the most prescribed combination therapies were CCB+BB and CCB+AA+D and the monotherapy was CCB. In Stage 5, the most prescribed combination therapies were CCB+AA+AB+BB, CCB+BB+AB and CCB+D. also the most prescribed monotherapy was CCB, BB and D.

Table 4: Antihypertensives used in Various Stages Of CKD

CLASS OF ANTIHYPERTENSIVE	NAME OF DRUG	NO. OF PRESCRIPTION
CCB (150)	Cilnidipine	65
	Nifedipine	60
	Amlodipine	24
	Benidipine	1
ALPHA AGONIST (57)	Clonidine	45
	Moxonidine	12
ALPHA BLOCKER (36)	Prazosin	36
BETA BLOCKER (70)	Metoprolol	37
	Atenolol	26
	Nebivolol	17
DIURETICS (54)	Spironolactone	23
	Torsemide	15
	Furosemide	16
ARB (20)	Losartan	12
	Telmisartan	8
ACEI (30)	Enalapril	17
	Ramipril	13

In this study, among CCBs most prescribed drug was cilnidipine. Clonidine was the most frequently prescribed alpha-agonist. Among alpha-blockers prazosin was most prescribed drug. Metoprolol was the most prescribed drug among beta-blockers. Among diuretics spironolactone was the frequently given diuretics. Losartan and enalapril was the most prescribed drugs among ARBs and ACEIs.

DISCUSSION

This study was done to analyse the prescribing trends of antihypertensives in chronic kidney disease patients with hypertension. This is a retrospective study conducted in 178 patients who were diagnosed with CKD and they were selected according to the inclusion and exclusion criteria. The data was collected from Nephrology department of Pushpagiri Medical College. A total of 178 cases of chronic kidney disease were retrospectively analysed, in which 107(60.1%) were males and 71(39.8) were females. On comparing the patients came for CKD treatment, male population were found to be in high proportion.72 patients were in age group 51-65 years and 68 patients in age group greater than 65 years. 35 patients were in age group 31-50 years and only 7 patients were in age group 18-30 years. Also, it was observed that 129 patients had diabetes mellitus, 80 patients had coronary artery disease and 35 patients had dyslipidaemia and 58 patients had eGFR less than 15, 39 patients had eGFR 30-59,32 patients had eGFR 60-89 and 14 patients had eGFR greater than 90ml/min/1.73m^2.Among 178 patients in the study 123 patients had albuminuria. In total 178 CKD patients were included in the study of which 14 patients had Stage 1, 32 patients had Stage 2, 35 patients had Stage 3, 39 patients had Stage 4 and 58 patients had Stage 5 CKD respectively. It is a global health problem and one of the risk factors for cardiovascular diseases. [4] Prevalence of CKD is on the rise and hence its management is very relevant. [11, 12] In this study, male preponderance was noted among CKD patients. Type 2 diabetes mellitus is a leading cause. Hypertension is a strong risk factor for CKD and the existing guidelines recommend strict antihypertensive treatment.

In this study number of antihypertensive drugs used in various stages of CKD was assessed. In total there is an increase in the number of drugs prescribed with more advanced stages of CKD. In stage 1 out of 15 patients ,8 was in mono therapy, 5 were in dual therapy and 1 patient was given triple therapy. In stage 2 out of 32 patients, 13 were in mono therapy, 16 were in dual therapy, and 3 patients was in triple therapy. In stage 3 out of 35 patients, 8 were in mono therapy, 20 were in dual therapy, 2 were in triple therapy and 5 patients were given quadruple therapy. In stage 4 out of 39

patients, 2 were in mono therapy ,21 was in dual therapy, 11 were in triple therapy and 5 patients were given quadruple therapy. In stage 5 out of 58 patients 1 patient was in mono therapy ,14 was in dual therapy, 32 were in triple therapy and 11 patients were in quadruple therapy. From this data it was found that presence of various co morbid factors and complications render polypharmacy inevitable.

In this study CCBs were the topmost prescribed class of antihypertensive drug irrespective of the stages. The most frequently prescribed CCB in this study was cilnidipine which is a new (fourth) generation DHP. [8,9,10] Cilnidipine blocks both L-type/N-type voltage gated calcium channels whereas other DHPs are strictly L-Type CCBs. By blocking the N-type channels in sympathetic nerves endings, cilnidipine suppresses the sympathetic over activity leading to dilatation of both afferent and efferent arterioles of the kidney and thus reducing intra glomerular pressure and proteinuria. [13,14] Cilnidipine significantly reduces urinary albumin creatinine ratio unlike other DHPs which increases proteinuria. Additionally, this drug reduced uric acid production without adversely affecting serum uric acid level and reduced urinary uric acid/ creatinine ratio. [15] In stage 1, alpha-blocker was the most prescribed after CCB and the least prescribed were diuretics and ACE-Is. In stage 2, alpha-agonist was the most prescribed after CCB and the least prescribed was beta-blockers. In stage 4, the least prescribed drugs were ACE-I and ARB. In stage 5, the second most prescribed drug is alpha-blocker and the least prescribed drug was ARB. There was a statistically significant difference in the prescribing trends of Diuretics, Alpha – blockers, Beta – blockers and Alpha- agonist in various stages of CKD.

Combination treatment is required for hypertension management in CKD according to the guidelines. Though various combinations were spotted, CCB+AA where a bit more frequently prescribed combination as alpha agonists interact minimally with other antihypertensive and they are valuable as adjunct therapy for resistant hypertension in CKD patients

CONCLUSION

CKD is a global health problem and one of the risk factors for cardiovascular diseases. Prevalence of CKD is on the rise and hence its management is very relevant. The rise in incidence is attributed to an aging population and increases with hypertension, diabetes, and cardiovascular disorders. The study was done to understand about the prescribing trends of antihypertensives in chronic kidney disease patients. The current study was conducted in department of Nephrology in Pushpagiri medical college hospital, Thiruvalla. 178 CKD patients who received

antihypertensive drugs were selected for the study. The patients' blood pressure, serum creatinine levels, eGFR and albuminuria were monitored in this study. The obtained parameters were analyzed and our study concluded that CCBs were the topmost prescribed class of antihypertensive drugs in all stages of CKD and CCB+AA was the most frequently prescribed combination therapy for CKD.

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ETHICS STATEMENT

Institutional Ethics / Human Ethics Committee approval was obtained with IEC no: PCP/IEC-01B/32/PD-2021, PCP/IEC-01B/29/PD-2021, PCP/IEC-01B/30/PD-2021, PCP/IEC-01B/31/PD-2021.

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