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PRESCRIBING PATTERN AND COST EFFECTIVENESS ANALYSIS OF ANTIHYPERTENSIVE DRUGS IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Introduction: Cost effectiveness analysis (CEA) is used to determine the clinical and economical effectiveness in Chronic Kidney Disease (CKD) patients. **Objectives:** To study the prescribing pattern of antihypertensive drugs in CKD and to analyse the cost effectiveness of drug therapies to manage hypertension in CKD. **Methodology:** A prospective, observational study in CKD patients in outpatient department of a tertiary care hospital. All CKD patients with a history of hypertension or diabetes mellitus or both were included. Patients with other causes were excluded. **Study procedure:** The prescriptions were screened to determine the prescribing pattern. The cost effectiveness of antihypertensive drugs was calculated using the incremental cost-effectiveness ratios. **Result:** The study was conducted in 200 patient in which majority were men. Mean of age and drugs per prescription was found to be 51.96 $\pm$ 12.67 and 6.49 ± 2.55 respectively. 37% and 32.5% of the study population was prescribed with two antihypertensive drugs and one antihypertensive drug respectively. Calcium channel blockers (70%) were the most prescribed class of antihypertensive drug. Amlodipine (44.5%) is the most prescribed antihypertensive agent. In patients who were on single antihypertensive drug, calcium channel blockers were found to be more cost effective. **Conclusion**: Use of antihypertensive drugs in CKD patients does not deviate from the guidelines laid down by National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines. Pharmacoeconomic analysis shows that Calcium channel blockers were the most cost effective antihypertensive in CKD patients when compared to other antihypertensive drugs when used alone.

KEYWORDS: Prescribing pattern, chronic kidney disease, cost effectiveness analysis.

INTRODUCTION

Chronic kidney disease (CKD), also called chronic renal insufficiency or progressive kidney disease, can be defined as a progressive loss of kidney function occurring over several months to years, and is characterized by the gradual replacement of normal kidney architecture with interstitial fibrosis.[1] Usually a GFR of >90 mL/min/1.73 m^2 is considered as normal kidney function. But, a patient can be diagnosed with CKD if the patient has proteinuria, haematuria, or evidence of structural damage from a kidney biopsy. Stage 5 CKD is referred to as end-stage renal disease (ESRD) or end-stage kidney disease. Hypertension (HTN) increases the risk of CKD. HTN generally develops concomitantly with progressive kidney disease. The direct adverse consequences of HTN on any vascular bed are expected to be a function of the degree to which it is exposed to the increased pressures. The pathogenic determinants of hypertensive renal damage can thus be broadly separated into 3 categories: (1) the systemic blood pressure (BP) "load"; (2) the degree to which such load is transmitted to the renal vascular bed; and (3) local tissue susceptibility to any given degree of barotrauma.[2]

Reflecting the expense associated with kidney replacement therapy, costs, and therefore cost effectiveness, of CKD therapies are largely driven by the ability to slow progression to kidney failure and limit time spent receiving dialysis. Better approaches to the management of both non-dialysis CKD and ESRD may offer the potential to slow the growth in costs or may otherwise offer 'value for money' in terms of improving clinical outcomes at a reasonable cost. Many health plans also now request evidence of both clinical and economic value for new therapies.

Pharmacoeconomics attempts to measure the benefit of one intervention is worth the cost of that intervention. This is very much important in making any critical pharmaceutical interventions regarding cost of health care. This study is aimed to investigate the pharmacoeconomic aspects of hypertension treatment in CKD patients.

MATERIALS AND METHODS

A prospective, observational study was carried out in the Department of Nephrology in a 650 bedded multi-specialty hospital located at Bangalore. The study was conducted for a period of six months from November 2013 to May 2014. Patients with CKD visiting outpatient department with a history of hypertension or diabetes mellitus or both were included in the study. Patients diagnosed to have CKD of undetermined etiology, drug induced CKD or nephrotic syndrome, drug overdose or poisoning cases and pregnant ladies who have CKD were excluded from the study.

The outpatient records of the patients were used to obtain the details of prescription. The following patient parameters were recorded: name, age, sex, outpatient number, diagnosis and relevant laboratory parameters. The drug parameters recorded were, brand name of the drug, strength, frequency and duration of administration. Patients receiving an antihypertensive medication with only one active ingredient were defined as receiving monotherapy. Those taking more than one active ingredient (either in one combination pill or in two different single pills) were defined as receiving combination therapy. The collected data was entered into MS Excel 2010 and results generated. The entire patients enrolled in the study was then categorised into those receiving monotherapy, two drug regimen, three drug regimen and four drug regimen respectively for pharmacoeconomic analysis. Patients receiving more than four drugs were not included in the study as the number of patients were insignificant.

The cost effectiveness of antihypertensive drugs in patients receiving a single drug was calculated using the incremental cost-effectiveness ratios (ICERs); where

$$\text{ICER} = \frac{\text{cost A} - \text{cost B}}{\text{effect A} - \text{effect B}}$$

Where, A is the most effective drug and B is the second most effective drug.

Cost of the drugs was obtained from Current Index of Medical Specialities (CIMS). Total drug cost of antihypertensive for a month was then calculated for individual patient and then the average cost was taken for the entire group. Effectiveness was taken as the value of maintenance BP on visit. Average of maintenance BP for that particular group receiving the same class of antihypertensive was taken and used for calculation. Cost effectiveness was then expressed as cost per drop in blood pressure and blood glucose achieved.

Before starting data collection and preliminary study, ethical clearance was obtained from Institutional Ethics Committee of M.S. Ramaiah Medical College and Hospitals, Bangalore.

RESULTS

During the study period, 200 prescriptions were included as per inclusion criteria, out of which 141 (70.5%) were males and 59 (29.5%) were females. Maximum number of patients, 66 (33%) were found between 51-60 years and minimum number of patients 1 (0.5%) between 11-20 years and 81-90 years. The maximum age of patients in the study population was 86 years and minimum age was 18 years. The mean age of the study population was found to be 51.96 ± 12.67. Out of 200 patients, 117 (58.5%) patients had HTN and 83 (41.5%) patients had both HTN and T2DM. The age categorization of the study population is shown in Table 1.

Table 1. Age categorisation of the study population

Age group (in years)	Number of patients (n=200)	Percentage (%)
11-20	1	0.5
21-30	10	5
31-40	32	16
41-50	41	20.5
51-60	66	33
61-70	40	20
71-80	9	4.5
81-90	1	0.5

Table 2. Total number of drugs prescribed per patient in the study population

Number of Drugs	Patients with HTN (n=117)	Patients with HTN + T2DM (n=83)	Number of Prescriptions (n=200)	Percentage (%)
1	5 (4.27%)	0	5	2.5
2-4	33 (28.21%)	4 (4.81%)	37	18.5
>5	79 (67.57%)	79 (95.19%)	158	79

HTN: Hypertension, T2DM: Type 2 Diabetes Mellitus

Table 3. Prescribing pattern of antihypertensive drugs

Antihypertensive drugs	Number of prescriptions	Percentage (%)
Calcium channel blocker	140	70
Diuretics	88	44
α agonist	74	37
α blocker	60	30
β blocker	32	16
Angiotensin receptor blockers	8	4
Angiotensin converting enzyme inhibitors	1	0.5

Table 4. Prescriptions with one antihypertensive drug

Antihypertensive drugs			Number of prescriptions	Percentage (%)
CCBS	Amlodipine	35	43	66.15
	Cilnidipine	6		
	Nifedipine	2		
Diuretic	Torsemide	10	11	16.92
	metolozone	1		
α agonist	Prazosin	5	5	7.69
β blockers	Metoprolol	3	5	7.69
	Bisoprolol	1		
	Nebivolol	1		
ARBs	Telmisartan	1	1	1.54

CCB - Calcium channel blockers, ARB - Angiotensin receptor blocker

Table 5. Prescriptions with two antihypertensive drugs

Two drug combinations	Number of prescriptions (n=74)
CCB+ α agonist	17
CCB+ Diuretic	14
CCB+ α blocker	9
CCB+ β blocker	6
Diuretic + α agonist	6
α blocker + α agonist	6
Diuretic + α blocker	5
Diuretic + β blocker	4
2 Diuretics	3
CCB+ ARB	2
Diuretic + ARB	1
Diuretic + ACEI	1

CCB - Calcium channel blockers, ARB - Angiotensin receptor blocker,
ACEI - Angiotensin Convering Enzyme Inhibitor

Table 6. Prescriptions with three antihypertensive drugs

Three antihypertensive drugs	Number of prescriptions (n=44)

CCB + α agonist + α blocker	15
CCB + Diuretic+ α agonist	7
CCB + Diuretic + α blocker	6
Diuretic + α agonist + α blocker	3
CCB + 2 Diuretics	3
CCB + α agonist+ β blocker	2
CCB + ARB + diuretic	2
CCB + Diuretic + β blocker	2
CCB + α agonist + β blocker	1
Diuretic + α agonist + β blocker	1
2 Diuretics + α blocker	1
Diuretic + β blocker + ARB	1

CCB - Calcium channel blockers, ARB - Angiotensin receptor blocker

Table 7. Prescriptions with four antihypertensive drugs

Four antihypertensive drugs	Number of prescriptions
CCB + Diuretic+ α agonist + α blocker	2
CCB + Diuretic+ α agonist + β blocker	3
CCB + Diuretic + α blocker + β blocker	2
CCB + 2 Diuretics + α blocker	1
CCB + α agonist + β blocker + α blocker	2
2 diuretics + α agonist + α blocker	3
2 diuretics + α blocker + β blocker	2
Diuretic+ α agonist + α blocker + ARB	1
Diuretic+ α agonist + α blocker + β blocker	1

CCB - Calcium channel blocker, ARB - Angiotensin receptor blocker

Table 8. Antihypertensive drugs prescribed in the study population

Generic drug	Number of prescriptions	Percentage (%)
Amlodipine	89	44.5
Cilnidipine	36	18
Nifedipine	15	7.5
Metoprolol	28	14
Nebivolol	1	0.5
Bisoprolol	3	1.5
Prazosin	60	30
Clonidine	74	37
Torsemide	69	34.5
Metolozone	17	8.5
Furosemide	13	6.5
Telmisartan	8	4
Ramipril	1	0.5

Table 9. Cost effectiveness analysis

Antihypertensive class	Number of prescription	Cost of drugs per 1 month	Average value of maintenance BP (mmHg)
Calcium channel blocker	43	177.48	132
Diuretics	10	317.2	136
β blocker	5	307.14	140
α agonist	5	88.62	145

The number of drugs prescribed for the study population was calculated and categorized. Single drug was prescribed to 5 (2.5%) patients. 2-4 drugs were prescribed to 37 (18.5%) patients and 5 or more than 5 drugs were prescribed to 158 (79%) patients. Mean number of drugs prescribed was found to be 6.49 ± 2.55 and highest number of drugs prescribed was found to 12.

The number of drugs prescribed to patients having only HTN was calculated and categorized. Single drug was prescribed to 5 (4.27%) patients, 2-4 drugs were prescribed to 33 (28.21%) patients and 5 or more than 5 drugs were prescribed to 79 (67.52%) patients. The mean drug per prescription in the study population was found to be 5.8 ± 2.55. The number of drugs prescribed to

patients having both HTN and T2DM was calculated and categorized. Among them 2-4 drugs were prescribed to 4 (4.81%) patients and 5 or more than 5 drugs were prescribed to 79 (95.19%) patients. The mean drug per prescription in CKD patients having both HTN and diabetes was found to be 7.5±2.57. The total number of drugs prescribed per patient in the study population is shown in Table 2.

Prescribing pattern analysis

Antihypertensive drugs used in the study population were identified and categorized (table 3). It was found that Calcium channel blockers 140 (70%), diuretics 88 (44%), α agonist 74 (37%), α blocker 60 (30%), β blocker 32 (16%), Angiotensin receptor blockers 8 (4%) and Angiotensin converting enzyme inhibitors 1 (0.5%) were the various antihypertensive drugs prescribed to the study population. Calcium channel blockers were the highest prescribed class of antihypertensive drugs and Angiotensin converting enzyme inhibitors were the least prescribed class of antihypertensive drugs in the study population. The prescribing pattern of antihypertensive drugs is explained in Table 3.

Categorization of study population according to the number of antihypertensive drugs prescribed

Prescribing pattern of antihypertensive drugs was analysed and it was found that 65 (32.5%) patients were prescribed with single antihypertensive, 74 (37%) patients were with two antihypertensive drugs, 44 (22%) patients received three antihypertensive drugs and 17 (8.5%) patients had four antihypertensive drugs. The mean of antihypertensive drugs per prescription was found to be 2.07 ± 0.94. The number of antihypertensive drugs per patient is explained in Table 2**.**

Single antihypertensive drug was prescribed to 65 (32.5%) patients (table 4). 43 (66.15%), patients were prescribed with CCBs, diuretics were received by 11 (16.92%) patients, 5 (7.69%) patients were given α agonist. β blockers were prescribed for 5 (7.69%) patients and ARB was given only to 1 (1.54%) patient. Patients who were taking only a single antihypertensive drug were found to be mostly on amlodipine (n=35) and torsemide (n=10). The prescription with one antihypertensive drug is explained in Table 4.

Two antihypertensive drugs were prescribed to 74 (37%) patients. CCBs with α agonist (n=17) and CCBs with diuretics (n=14) were the most prescribed combinations in two- drug regimen. The prescription with two antihypertensive drugs is explained in Table 5.

Three antihypertensive drugs were prescribed to 44 (22%) patients in the study population. Calcium channel blocker with α agonist and α blocker is the most prescribed combination. Prescriptions with three antihypertensive drugs are explained in Table 6.

Four antihypertensive drugs were prescribed to 17(8.5%) of the study population. The Prescriptions with four antihypertensive drugs is provided in Table 7.

Antihypertensive drugs prescribed in the population

The various antihypertensive drugs prescribed in the study population were identified. Amlodipine was given to 89 (44.5%) patients, cilnidipine for 36 (18%) patients, 15 (7.5%) patients received nifedipine, metoprolol 28 (14%) patients, nebivolol 1 (0.5%) patient, bisoprolol 3 (1.5%) patients, prazosin for 60 (30%) patients, clonidine 74 (37%) patients, torsemide 69 (34.5%) patients, metolazone 17 (8.5%) patients, furosemide 13 (6.5%), telmisartan 8 (4%) and ramipril 1 (0.5%) were the various antihypertensive drugs used in the study population. Amlodipine was found to be prescribed more in number 89 (44.5%). Ramipril and nebivolol was found to be the least prescribed 1 (0.5%) antihypertensive. The antihypertensive drug prescribed in the study population is explained in Table 8.

Cost effectiveness analysis

Analysis for CE was carried out in a total of 63 CKD patients receiving a single drug for elevated blood pressure. The major classes of antihypertensive drugs prescribed in this population were CCBs (43), diuretics (10), β- blocker & α agonist for 5 patients each.

The average cost of each class of drug was calculated in Indian Rupees and average value of maintenance BP after receiving the drug was taken for effectiveness calculation.

$$\text{ICER} = \frac{[\text{Cost of Drug A} - \text{Cost of Drug B}]}{[\text{Effect of A} - \text{Effect of B}]}$$

(Where, A = Most effective therapy, B = 2nd most effective therapy).

Of all the four prescribed regimens CCBs were found to be most effective and diuretics were the second most effective class of antihypertensive. Incremental Cost Effectiveness Ratio was calculated and it was found that Rs.31.75 was extra required while using diuretics than CCBs for achieving respective maintenance value.

DISCUSSION

The findings of the prescription pattern study conducted in a tertiary care hospital, Bangalore gives an idea about the demographic data, drugs prescribed and cost of drugs in CKD patients. CKD was found to be more in males (70.5%) due to various risk factors like smoking, drinking alcohol, HTN, diabetes etc. A study conducted by Karthikeyan et al[3] also reported that males were more likely to get CKD. Mean age of the study population was 51.96± 12.67. Mean age is similar to that of the mean age (50.9±13.6) in the study conducted

by Karthikeyan et al[3] and in the study by Bajait et al[4] in India.

CKD Patients usually follow multiple medication regimens due to many comorbid conditions like phosphate retention, mineral imbalance, vitamin deficiency, anaemia, dyslipidaemia, heart diseases, hypothyroidism etc. So apart from antihypertensive drugs and antidiabetic drugs, patients have to take phosphate binders, mineral supplements, vitamin supplements, antiplatelets etc. Because of this polypharmacy can be seen in majority of the patients. 79% of the total population are on polypharmacy. It was found that average of 7 drugs was consumed by the study population. The result was compared with the study conducted by Rowa Al-Ramahi[5] and it was found to be greater than what we observed in our study. All the patients in the study had HTN. HTN can be either a cause or a complication of CKD. HTN is also a risk factor for progression of kidney disease and chronic vascular diseases. T2DM can lead to diabetic nephropathy if the blood sugar level is uncontrolled. Diabetic nephropathy is one of the leading causes for CKD. It can also occur as a comorbid disease.

Antihypertensive drugs are given to CKD patients to reduce the blood pressure, to reduce the risk of chronic vascular disease and to slow the progression of CKD. K/DOQI guideline on HTN and antihypertensive agents in CKD proposes recommendations on the use of antihypertensives in all patients with CKD, whether or not they have HTN. The Seventh Joint National Committee (JNC-7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a goal blood pressure of <130/80 mm Hg for patients with CKD.[6] The mean number of antihypertensives used in CKD patient was 2.07 ± 0.94 and was lower (2.3±0.5) than that reported by Karthikeyan et al.[3] Elevated blood pressure is often more difficult to control in patients with CKD than in those with normal kidney function. Therefore, to achieve adequate blood pressure, two or more different blood pressure medications are usually required.

CCBs were found to be more used in the study population followed by diuretics. This was contrary to the study conducted by Bajait et al[4], where diuretics are more used than CCBs. CCBs control the blood pressure and have renoprotective effect. Its effectively reduces systemic blood pressure while maintaining the glomerular filtration rate and effective renal plasma flow.

Pharmacokinetic parameters of CCBs are unaltered in CKD patients and are little dialyzable. Hence, dosage adjustment is not required in the case of CCBs. This makes them favourable in the final stage of CKD. Amlodipine was the most used antihypertensive agent. Diuretics are generally necessary in CKD for control of extracellular fluid volume expansion and for their associated effects on blood pressure. Fluid retention is one of the complications of HTN in CKD patients. So patients require diuretics to reduce the blood pressure. Loop diuretics (torsemide & furosemide) are more used than thiazide diuretics. Former is recommended in the final stages (stage IV &V) and latter is recommended in the initial stages (stage 1-3) according to K/DOQI guideline.[6] Thiazide diuretics, with exception of metolazone, are ineffective in CKD stages 4 and 5 due to thiazide's inability to reach the site of action. Torsemide, furosemide and metolazone are the diuretics used in the CKD patients of this study. β blockers are used in CKD patients who are also having myocardial infarction. Metoprolol is the most prescribed β blocker used in the study population. Metoprolol is a lipid soluble β blocker which does not require dosage adjustment which makes them preferable in CKD patients. ACEIs and ARBs, which are preferred drug in initial stages of CKD, can cause hyperkalemia in end stages of CKD. Dose adjustment is also required for ACEIs and ARBs in chronic renal failure due to the altered pharmacokinetic parameters. Hence ACEIs and ARBs are least preferred in end stages of CKD patients.

Results from the CEA of antihypertensive drugs in patients receiving a single antihypertensive drug shows that CCBs appears to be a cost-effective and perhaps cost saving, alternative to diuretics. To our knowledge this analysis is the first to access cost effectiveness of antihypertensive drugs in patients with CKD. Other studies have evaluated the cost effectiveness of antihypertensive drugs in different clinical scenarios.

CONCLUSION

Analysis of 200 prescriptions revealed that combination therapy was more preferred than single drug therapy. CCBs were the most commonly prescribed antihypertensive drug in CKD patients. All the patients in the study population had hypertension. Pharmacoeconomic analysis shows that CCBs were the most cost effective antihypertensive in CKD patients when compared to other antihypertensive modalities. Use of antihypertensive in CKD patients does not deviate from the guidelines laid down by NKF KDOQI guidelines.

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