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A PROSPECTIVE STUDY ON ADVERSE DRUG REACTIONS IN CHRONIC KIDNEY DISEASE PATIENTS WITH HYPERTENSION

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ABSTRACT

Hypertension (HTN) is very frequent in patients with renal disease and its prevalence increases as chronic renal failure (CRF) progresses. The prevalence of HTN in renal patients depends fundamentally on the degree of the renal failure and the type of nephropathy, but varies also, as in essential HTN, with age, sex, and body mass index. **Objectives:** The main objective of the study was to assess the adverse drug reactions in kidney disease patients with hypertension. **Materials and Methods:** The study was carried at Nephrology department of K R Hospital, Mysore, Karnataka, from April 2020 to September 2020. A total of 84 patients were enrolled in the study as per the inclusion and exclusion criteria. Patient's demographics data were collected using data collection forms. The adverse drug reactions were analyzed by using Naranjo causality assessment scale and Hartwig's severity assessment scale. **Results:** Out of 84 candidates, females show dominance over males. 14 were presented with ADRs (16.7%). Hypokalemia, vomiting & headache and interstitial nephritis were the most commonly reported ADRs. 57.1% of ADRs were mild and 42.9% were moderate. 42.9% of ADRs were probable and 57.1% were in the possible category. **Conclusion:** The study was conducted to assess the adverse drug reactions found in hypertensive kidney patients. It can be reduced by pharmacist intervention, providing education and awareness about the disease and importance of medication adherence among the study population.

KEYWORDS: Adverse drug reaction (ADR), Chronic Kidney Disease (CKD), Hypertension (HTN) hypokalemia, interstistial nephritis.

INTRODUCTION

Chronic Kidney Disease is defined as the presence of reduced kidney function[1] (an eGFR <60mL/min/1.73m^2) or kidney damage for ≥3 months duration. Hypertension, defined by European Society of Hypertension as a blood pressure of ≥140/80 mmHg affects almost 30% of the general adult population and up to 80% of those with CKD.[2,3]

Patients with CKD are often given several medications for the management of the disease, its complications and other co-morbidities. Hence CKD patients are particularly at the increased risk of ADR as they usually follow multiple drug regimens, co-morbidities and due to the changes in pharmacokinetic and pharmacodynamics parameters.

Poorly controlled hypertension is a major risk factor in non-dialysis chronic kidney disease (CKD) and its prevalence increases as chronic renal failure progresses. The prevalence of HTN in renal patients depends fundamentally on the degree of the renal failure and the type of nephropathy, but varies also, as in essential HTN, with age, sex, and body mass index. Strict control of blood pressure (BP) is, therefore, essential in avoiding or delaying the decrease in renal function as well as reducing cardiovascular risk. Current guidelines for CKD patients recommend an office blood pressure (BP) target and its 130/80 mmHg and 125/75 mmHg if proteinuria is higher than 1 g/day. However, HTN in these patients is difficult to control and usually requires the use of various drugs.[6,7]

Hypertension is a major risk factor for cardiovascular and renal disease. Conversely, chronic kidney disease (CKD) is the most common form of secondary hypertension and mounting evidence suggests it is an independent risk factor for cardiovascular morbidity and mortality. The prevalence of CKD has been better characterized since the National Kidney Foundation

issued a standard classification based on the level of glomerular filtration rate (GFR) and the presence or absence of evidence of renal injury. Patients with stage 1 and 2 CKD need to show evidence of renal injury (e.g., proteinuria), and GFR of >/=90 and 60-89 mL/minute, respectively. Stages 3, 4, and 5 correspond to GFR 30-59, 15-29, and <15mL/minute, respectively, regardless of any other evidence of renal damage.[8]

Moderate to severe CKD (stage 3 or greater) as defined by a glomerular filtration rate (GFR) <60 ml/minute/1.73 m^2 is strongly associated with new cardiovascular events. Estimated GFR (eGFR) derived from formulas such as the Modification of Diet in Renal Disease (MDRD) equation is superior to serum creatinine alone in the diagnosis of CKD. Prevalence of stage 3 CKD (GFR 30-59 ml/min/1.73 m^2) is described by using MDRD equation among participants >/=65 years with normal and elevated serum creatinine and by specific chronic condition.[9]

According to WHO, ADR is defined as "a response to a drug which is noxious and unintended, which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function".

The causality to a suspected adverse drug reactions can be attributed by timing, the pattern of illness, the results of investigations, and rechallenge. The management of ADRs are complicated one as they increases the costs due to increased hospitalization, prolongation of hospital stay, additional investigations, and drug therapy in more serious cases. So it is necessary to detect the ADRs and the risk associated with the use of drugs earlier, during the ADR monitoring and reporting program. Thus, Pharmacovigilance Programme of India has launched in June 2010 to ensure the safety of the drug and to promote ADR data in Indian patients.

MATERIALS AND METHODOLOGY

This is a hospital based prospective observational study. It was conducted at Nephrology department of K R Hospital, Mysore. The study duration was a period of six months from April 1st 2020– October 1st 2020. The data were collected from the patient case records and other relevant sources after getting informed consent. During the study period, we attended 84 patients of age group between 18-85 years old. The patients who were pregnant, pediatrics and those who have undergone dialysis were excluded from the study.

Ethical approval was obtained from the Institutional Ethical Committee of Mysore Medical College and Research Institute, K R Hospital; Mysuru.

Importance of the study was explained to the participants and informed consent was retrieved from all the subjects participated in the study. The data collected from the patients from questionnaire and data collection form. The statistical analysis was done by using SPSS and analyzed using the statistical like ANOVA and two-tailed t-test and the results were compared.

RESULTS

Demographics

Table 1: Gender distribution in the study population.

Gender	No of Patients	Percentage
Male	16	19%
Female	68	81%
Total	84	100%

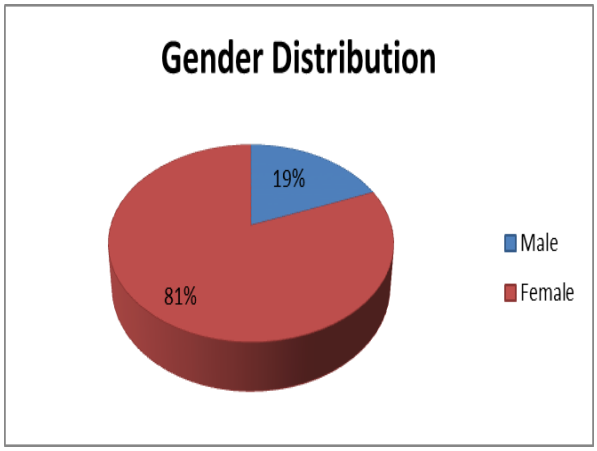

Figure 1: Gender distribution in the study population.

Table 1 and Figure 1 shows greater dominance of females over males in the study population. Among 84 patients included in the study, 16 were males (19.0%) and 68 were females (81%).

Table 2. Age categorization in the study population

Age	Number of patients	Percentage
18-24 yrs	1	1.2%
25-34 yrs	1	1.2%
35-44 yrs	2	2.4%
45-54 yrs	6	7.1%
55-64 yrs	8	9.5%
65-74 yrs	33	39.3%
>74 yrs	33	39.3%
Total	84	100%

Table 2 point out that the most of the patients were in the age group of 65-74 (39.30%) and in the age group of > 74 years (39.30%) and the least were in the age group 25-34 yrs (1.2%) and 18-24 yrs (1.2%).

Table 3: Prevalence of Hypertension in the study population.

Diagnosis	Number of patients	Percentage
CKD with HTN	74	88.1%
CKD without HTN	10	11.9%
Total	84	100%

Table 3 shows most of the CKD patients have Hypertension (88.1%).

Table 4: Social history in the study population.

Social History	Number of patients	Percentage
Alcohol	5	6%
Smoking	13	15.5%
Smoking and alcohol	4	4.8%
None	62	73.8%
Total	84	100%

In our study, **Table 4** indicates that social history has no major role in the occurrence of HTN in CKD patients.

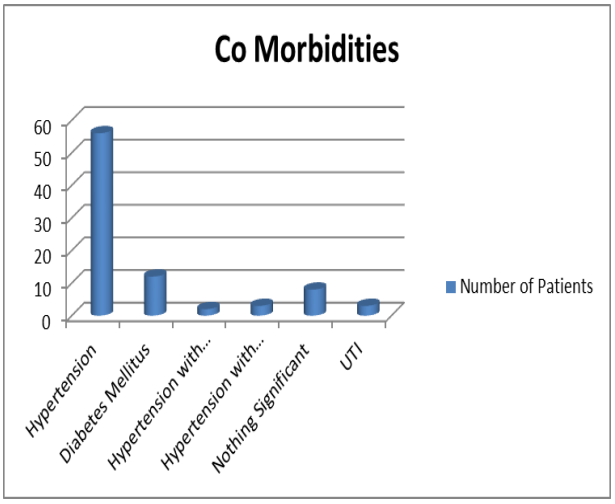

Figure 2: Co-morbidities in the study population.

Figure 2 point out most of the CKD patients have HTN (66.7%) as co morbid condition followed by Diabetes mellitus (14.3%).

Adverse Drug Reaction

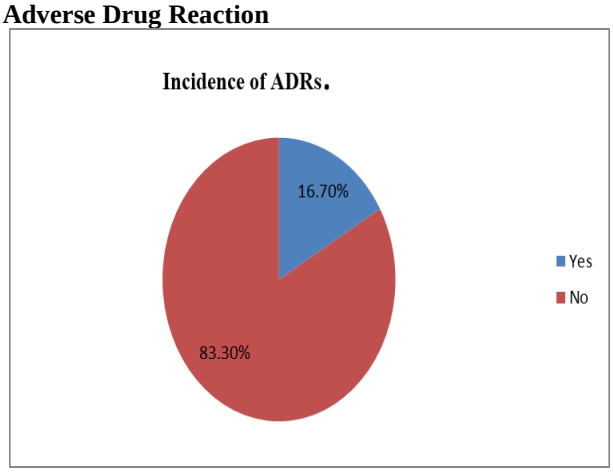

Figure 3: Incidence of ADRs.

Out of 84 patients, 14 patients (16.7%) are observed with ADR and 70 patients (83.3%) are without ADR. The details are represented in the **Figure 3**.

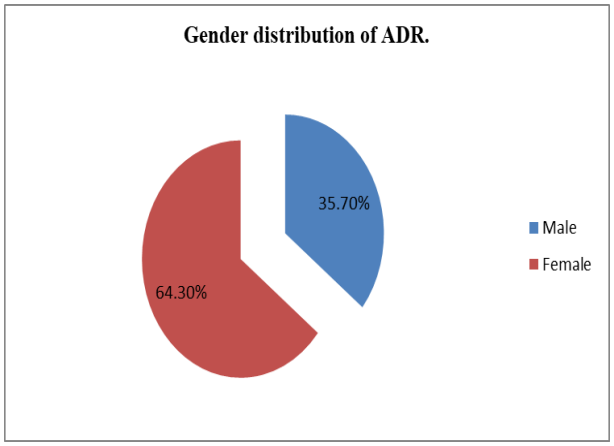

Figure 4: Distribution of adverse drug reactions based on gender.

Figure 4 shows that the female patients (64.3%) are more prone to ADR than male patients (35.7%).

Table 6: Distribution of ADRs based on age group.

Age group	Frequency	Percentage
45-54 yrs	1	7.1%
55-64 yrs	3	21.4%
65-74 yrs	4	28.5%
>74 yrs	6	43.0%
Total	14	100%

From the **Table 6**, it is observed that ADR occurrence is more in the age group < 74 yrs (43.0%)

Table 7: Suspected adverse reactions in the study population.

Suspected ADR	Frequency	Percentage
Vomiting and headache	3	21.4%
Hypokalemia	3	21.4%
Interstitial disease	3	21.4%
Diarrhea	1	7.1%
Hyponatremia	2	14.3%
Indigestion , hyperglycemia	1	7.1%
Dizziness	1	7.1%
Total	14	100%

From the **Table 7**, it is understood that the most commonly reported ADR is hypokalemia (21.4%), vomiting & headache(21.4%) and interstitial disease(21.4%) followed by hyponatremia (7.4%), indigestion & hyperglycemia(7.1%)dizziness(7.1%) and diarrhea(7.1%).

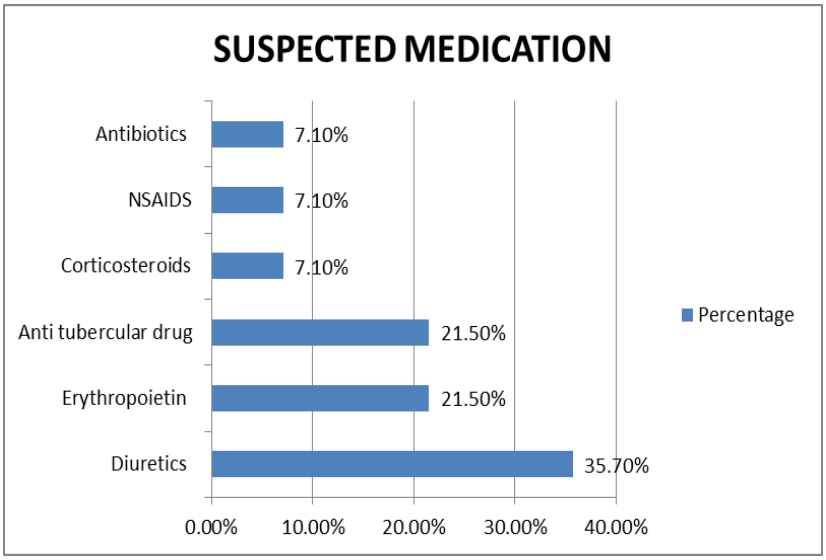

Figure 5: Suspected medication in the study population.

Figure 5 shows that, among the study population, the mostly suspected drug class causing ADR is diuretics 35.7% (n=5), followed by 21.5% erythropoietin and antitubercular drug each (n=3) and 7.1% corticosteroids, NSAIDs and antibiotics each (n=1)

Table 8: Suspected ADRs according to medication.

Suspected medications	Suspected ADR	Frequency
Diuretics	Hypokalemia Hyponatremia	3 2
Erythropoietin	Vomiting and headache	3
Anti-tubercular drug	Interstitial disease	3
Corticosteroids	Indigestion, hyperglycemia	1
NSAIDS	Dizziness	1
Antibiotics	Diarrhea	1
Total		14

Table 9. Outcomes of reaction in the study population

Outcomes of reaction	Frequency	Percentage
Recovered	12	85.8%
Recovering	2	14.2%
Total	14	100%

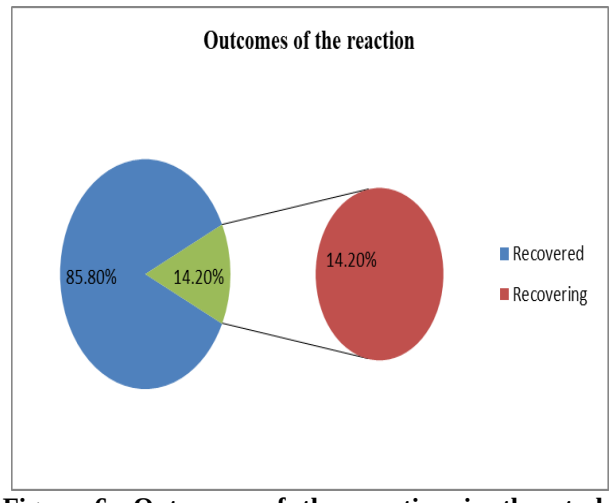

Figure 6: Outcomes of the reaction in the study population.

Table 9 and Figure 6 shows the outcome of the reaction in the study population. Majority of the patients (85.8%) were recovered. Among 14 ADR found in the study population, the Naranjo scale assessment provides 42.9% of ADRs are probable and 57.1% are possible.

Table 10: Naranjo causality assessment scale in the study population.

Naranjo causality assessment scale	Frequency	Percentage
Probable	6	42.9%
Possible	8	57.1%
Total	14	100%

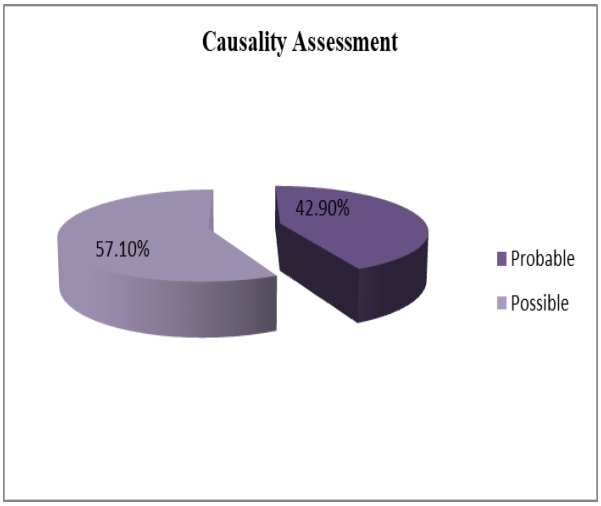

Figure 7. Causality assessment in the study population.

Table 11: Hartwig's assessment scale in the study population.

Severity	Frequency	Percentage
Mild	8	57.10%
Moderate	6	42.90%
Total	14	100%

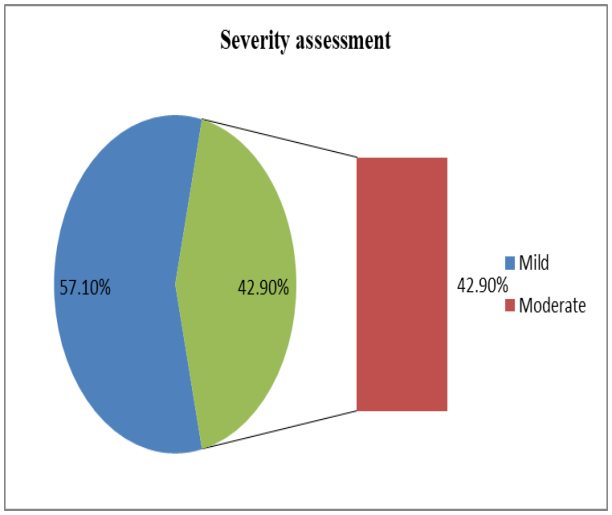

Figure 8: Hartwig's assessment scale in the study population.

Table 11: and figure 8 shows that out of 14 ADR, 57.10% of ADRs were mild and 42.90% were moderate.

DISCUSSION

Demographics

The present study set out to assess the adverse drug reaction in chronic kidney disease patients with hypertension. The study was carried out in the nephrology department of K R Hospital, Mysore over a period of 6 months.

Out of 84 patients reviewed, we found that female patients (81%) were predominant while comparing to male patients (19%). This was contradictory with the study results of **Laville S M. et al.**[4] In this study, 65% were male patients and 35% were female patients.

In our study, majority of the patients (78.6%) belongs to the age group of >64 years and the least number (1.2%) of patients is in the age group of below 34 years. The result pointed out the increased incidence of hypertension among older patients. This result is consistent with the study of **Kareem S.A. et al**., which reported a linear increase in the prevalence of hypertension with chronic kidney disease. The mean age in the study population was found to be 60.[5]

On the review of the social history of the study population, it is found that 15.5% of the patients had the habit of smoking, 6.0% were alcoholics and 4.8% of the patients had both habits. Majority of the patients (73.8%) were neither smokers nor alcoholics.

Our study showed that the most patients with CKD have co morbidities. Among the total study population, 76 (90.5%) were found with the co-morbidities such as hypertension (66.7%), diabetes mellitus (14.3%), HTN with anemia (2.4%), HTN with TB (3.6%), and urinary tract infection (3.6%). This shows hypertension to be the most commonly occurring co morbidity followed by diabetes mellitus. The frequency of other co morbidities is less in the population. This result was comparable with a study by **Kareem S A et al.** The most prevalent co morbidities were hypertension, diabetes mellitus, metabolic syndrome and other cardiovascular diseases.[5]

Adverse drug reaction

People with CKD are usually in advanced ages and also pharmacotherapy in CKD commonly involve polypharmacy. Hence they are at high risk of developing ADR.

Out of 84 patients, 14 patients (16.70%) reported ADR, in which 5 are male patients and rest are female which is supported by the study conducted by **Tran C et al**.[10] But this is contradictory with the result of study conducted by **Laville S M et al.**[4]**,** which reported higher prevalence of ADR among male patients with CKD.

Among the study population, most commonly reported ADR were hypokalemia, Vomiting & headache and Interstitial disease. Drug class contributing majorly to ADRs is Diuretics (35.70%). Other major drugs causing ADRs are Erythropoietin (21.50%), Anti tubercular drugs (21.50%), Corticosteroids (7.10%), NSAIDs (7.10%) and Antibiotics (7.10%). This is similar to a study carried out by **Kareem S A et al**[5], in which the most common drug contributing to the ADR are diuretics (69%).

Our study results which were observed by Naranjo Causality assessment scale shows that 57.10% were "possible" and 42.90% were "probable" ADRs. On the contrary, in the study conducted by **Kareem S A et al.**[5]

In their study Naranjo algorithm, showed 57.8% "possible".

Hartwig's severity assessment scale shows 57.1% of the total ADRs are mild and 42.90% are moderate. A similar result is reported in a study conducted by **Kareem SA et al,** in which most of the reported ADRs were considered to be mild or moderate. About 59% of ADRs were mild in their study.[5]

An association is found between the BP control and family history with the ADR, whereas the association of gender, age, economic status, and marital status and co morbidity with ADR is not significant.

CONCLUSION

ADRs are associated with considerable morbidity, mortality and high medical cost. Polypharmacy is common in patients with CKD. So they are at high risk of developing ADR. Careful therapeutic monitoring and dose individualization is necessary to minimize the incidence of ADR.

In our study out of 84 patients, 14 patients are observed with ADR, in which 5 are male patients and 9 are female. The most common reported ADR is hypokalemia. Diuretic is the major drug class contributing to ADR. All the reported ADRs are categorized as mild and moderate. Naranjo causality assessment provides all the reported ADRs come under probable and possible. The association of BP control and family history were found to be statistically significant in our population.

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