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Research Article

Polypharmacy and potential drug-drug interactions among medications prescribed to chronic kidney disease patients

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ABSTRACT

Background and Objectives: Chronic kidney disease is a major systemic condition. Presence of comorbid conditions with the deteriorating renal function, lead them to use multiple drugs. Polypharmacy is common among chronic kidney disease. The possibility of drug interaction rises when a patients concurrently receive more than one drug and the chances increase with the number of drugs taken, which may be associated with increased morbidity, mortality, length of hospital stay and health-care cost. The aim of this study was to assess the polypharmacy and pattern of drug- drug interactions in chronic kidney disease patients attending OPD and ward of nephrology unit in Kathmandu Medical College teaching hospital.

Material and Methods: This was a prospective cross sectional study conducted among 143 chronic kidney disease diagnosed patients in Kathmandu Medical College Teaching Hospital. The Lexi-comp database was used to evaluate patient's medications for potential drug-drug interactions.

Results: Chronic kidney disease was predominant among male (65.7%) than the female (34.3%). The most common age group was 41-60yrs followed by 61-80 yrs. The mean age of the patients was 54.38 ± 16.43 years. Chronic kidney disease was associated with multiple co-morbid conditions. The most common comorbid conditions were hypertension 52 (36. 4%) and hypertension and diabetes both in 42 (29.4%). A total of 143 prescriptions were included in this study. Average number of drugs per prescription was 6.1. Almost 5-8 medicines per prescription were observed among 95(65.73%) patients. A total of 837 medicines were prescribed. A total number of 206 potential drug-drug interactions were observed among 143 patients. Depending upon the risk rating categorize, the most common were, risk rating C 178(86.4%) and the most frequent drug interaction was between amlodipine and calcium carbonate 65 (45.45%) .

Conclusion: The prevalence of potential drug-drug interaction is high among chronic kidney disease patients. About 63% of interactions have moderate severity. The safest approach to avoid potentials drug-drug interaction is the implementation of appropriate guidelines, detailed and rationalize knowledge of drugs and to utilize available drug-drug interaction software to avoid harmful drug-drug interaction among chronic kidney disease patients.

Keywords: Chronic Kidney Disease, Drug-drug interaction, Polypharmacy

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INTRODUCTION

Drug interaction has occurred when the administration of one drug increases or decreases the beneficial or adverse responses to another drug [1]. The possibility of drug interactions arises when a patient concurrently receives more than one drug, and the chances increase with the number of drugs taken [2].

Polypharmacy can be defined as the concurrent use of more than five different medications by a patient for the treatment of a particular disease or group of disease. The consequences of polypharmacy include adverse effects, drug-drug interactions (DDIs), non-compliance and may lead to higher health-care costs and an increased risk of hospitalization [3]. The frequency and severity of potential drug-drug interaction (pDDIs) could be affected by the type and number of drugs per patient, which at the same time, could be influenced by comorbidities [4].

Chronic kidney disease (CKD) is a major health problem worldwide due to its increasing incidence, prevalence, and associated high burden [5, 6]. It is estimated that the prevalence of CKD is around 10.6% in urban areas of Nepal [7]. The prevalence of DDIs in CKD patients from previous studies ranged between 56.9% and 80.8 [8-12].

Chronic kidney disease (CKD) can be defined as a progressive and irreversible deterioration in the renal function of an individual over a period of at least 3 months regardless of the underlying etiology [13]. The common causes of CKD are hypertension, diabetes mellitus, interstitial diseases, glomerular diseases [14]. Management of these comorbidities and risk factors is important in retarding progression of CKD and reducing mortality [6, 15-16]. Multiple drugs are combined in the treatment of CKD patients which can produce drug interactions with expected beneficial effects, but in some cases undesired outcomes may also occur, such as ineffective treatment and severe adverse effect hence, polypharmacy is often practiced [17-19].

Kidney is the major route of elimination so it plays a central role in excretion of many metabolic breakdown products, including ammonia and urea from protein, creatinine from muscle, uric acid from nucleic acid, drugs and toxin [20]. The drugs which are excreted unchanged in urine should be avoided or dose should be reduced in renal impairment because renal impairment may causes drugs or their metabolites to accumulate which lead to develop toxicity [20- 21].

Before prescribing medicines, the prescriber always estimate renal functions especially to those drugs which are excreted through kidney or that can able to impair renal function or nephrotoxic and also consult a reference on drug dosing in renal failure [21].Prescriber should know all drugs taken by patients including drugs prescribed by other prescribers and all over the counter drugs, herbal products and nutritional supplement [22]. By taking a careful drug history the adverse consequences of DDI can be avoided [14].

DDIs are major clinical problem among CKD. Medication review is an essential part in the CKD patient to avoid adverse effects that can be caused due to polypharmacy and drug-drug interactions. This study was designed to assess the polypharmacy and drug-drug interactions in chronic kidney disease patients.

MATERIALS AND METHODS

The cross-sectional observational study among 143 patients was conducted at the nephrology unit of Kathmandu Medical College for a period of 1 year (Feb 2019-March 2020). Before starting

the study ethical committee clearance was obtained from Institutional Review Committe Kathmandu Medical College.

Purposive sampling technique was used for the selection of cases. The patients age 18yrs or above and having diagnosed chronic kidney disease, treated in OPD or ward of medicine under nephrology unit were included in this study. A data collection form was used to collect data from the patient prescription and medical record. Data included age, gender, comorbidities, CKD stages, drug (dose, route, frequency) All collected data were subjected to drug-drug interaction analysis by using Lexi-comp (A software program of drug interaction). This software provides the severity, risk rating and the summary of drug-drug interaction. The risk rating is categorizes as A, B, C, D, X. Risk rating A means no known interaction, for B no action is needed, C requires to monitor therapy, D requires to consider therapy modification, while X means we should avoid combination. Statistical analysis was performed using SPSS version 16.0.

RESULTS

A total of 143 patients were included in the study. Among them, 94(65.7%) were male and 49 (34.3%) were female. The mean age of study population was 54.38 $\pm$ 16.435 years and the maximum age was 86years. The common comorbidities present among CKD patients were hypertension 51 (35.7%) followed with hypertension and diabetes both 34 (23.8%). Depending upon the stages of CKD the maximum number of patients belong to stage V 119 (83.2%). Table 1 shows the demographic detail of patients.

During study period, 837 drugs were prescribed with an average of 6.1 drugs per prescription. The most commonly prescribed medications were amlodipine 100 (69.93 %) followed by torsemide 87 (60.84%), calcium carbonate 86 (60.14%), ferrous ascorbate 85 (59.44%).

Table 1: Demographic status of patients suffering from chronic kidney disease

Titles	Number	Percentage (%)
Age		
<30	19	13.29%
31-60	66	46.15%
>80	58	40.56 %
Gender		
Male	94	65.7%
Female	49	34.3%
CKD Stages		
Stages V	119	83.2%
Stages IV	7	4.9%
Stages III	9	6.3%
Stages II	5	3.5%
Stages I	3	2.1%
Co morbidities		
None	24	16.8%
HTN	52	36.4%
DM	5	3.5%
HTN & DM	42	29.4%
HTN & Others	8	5.6%
DM & Others	4	2.8%
Others	8	5.6%
Total Patients	143	
Mean Age ($\pm$ SD)	54.38 $\pm$16.43	
Range of age	18 yrs -86yrs	

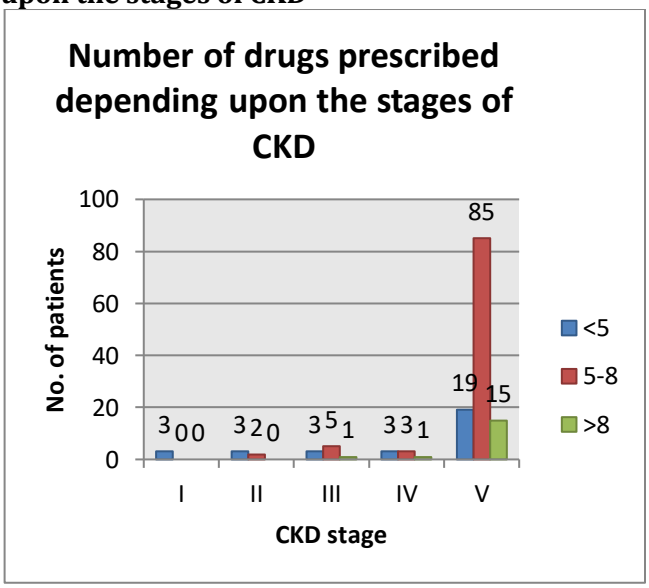
Table 2: Distribution of patients by number of drugs administered

Number of drugs administered	Number of patients	Percentage
<5	31	21.68%
5-8	95	66.43%
>8	17	11.89%
Number of drugs administered per patients - minimum-2 and maximum-11		

Among 143 CKD patients, 31(21.68%) were taking less than five drugs per day, 95 (66.43%) were taking 5-8 drugs per day and 17(11.89%) were taking more than 8 drugs per day shown in Table 2.

Out of 143 CKD patients, 119 patients were on stage 5 and they were taking more drugs as compare to other stages of CKD shown in Figure 1.

Fig 1: Number of drugs prescribed depending upon the stages of CKD



A total of 206 potential drug interactions were identified in 112 CKD patients. Among the total drug interactions, according to risk rating classification,178 (86.4%) were C, 20(9.7%) were B,7 (3.3%) were D and 1 (0.5%) was X risk rating. The overall prevalence of DDIs was 78.3%. Table 3 show the incidence of potential drug-drug interaction of different risk rating.

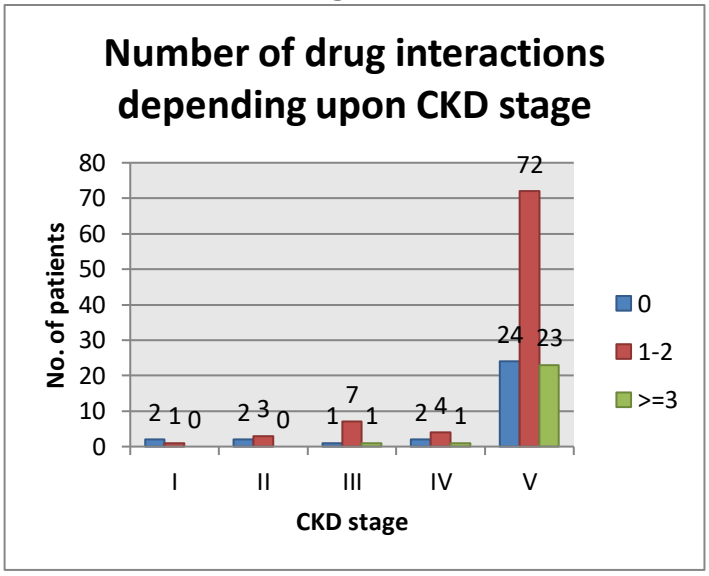
The most common interacting pair among 112 patients was amlodipine with calcium carbonate and next was amlodipine with calcium acetate shown in Table 4. Depending upon the stages of CKD, stage 5 had more drug interactions as compare to other stages as shown in figure 2.

There were total 119 CKD stage 5 patients and among them 24 patients had no interaction, 72 had 1-2 interactions and 23 had more than or equal to 3interactions.The total number of drug-drug interactions were 95 among stage 5.

Table 3: Incidence of potential drug-drug interaction of different risk rating

Drug-drug interaction risk rating	No of incidences	Percentage
B	20	9.7%
C	178	86.4%
D	7	3.3%
X	1	0.48%

Fig 2: Distribution of patients by number of drug interaction in each CKD stage



The multivariate regression analysis showed that increased number of medication was associated with the occurrence of drug interactions (r-0.310, p-<0.0001). The variance inflation factor was from 1.096 to 1.375 which indicated absence of multi-co-linearity between independent variable. The age of patient and number of comorbidities were not associated with the occurrence of drug interactions shown in Table 5.

Table 4: Most common potential drug-drug interactions

Drug combination	Risk Rating	Incidence of interaction	Percentage of patients having DDIs
Amlodipine+Calcium Carbonate	C	65	58.03%
Amlodipine+ Calcium Acetate	C	28	25.0%
CalciumCarbonate+ Calcitriol	C	22	19.64%
Linagliptine+Torsemide	C	18	16.07%
Torsemide+aspirin	C	12	10.71%
Calcium Carbonate+ Aspirin	B	9	8.03%
Levothyroxine+PPI	B	6	5.35%
Calcium Acetate+Calcitriol	B	5	4.46%
CalciumCarbonate+ Metazone	C	5	4.46%
Linagliptine+ Furosemide	C	5	4.46%

Table 5: Multivariate analysis of factors associated with potential drug-drug interactions

Factors	Standardized coefficient	P-value	95% Confidence interval for B	
	Beta		Lower bound	Upper bound
Age	0.098	0.181	-0.003	0.018
No. of co-morbidities	0.089	0.279	-0.105	0.361
No. of medications used	0.490	<0.001	0.199	0.389

Table 6: Nephrotoxic drugs

Drug Class	**Drug name**	**Number (%)**	**Pathophysiologic mechanism of renal injury**
Diuretic	Furosemide	25 (17.48%)	Acute interstitial nephritis
	Torsemide	87 (60.84%)	
Angiotensin II Blocker	Losartan	5 (3.5%)	Altered intraglomerular hemodynamics
	Telmesartan	4 (2.8%)	
	Irbesartan	1 (0.7%)	
NASID	Aspirin	17(11.89%)	Chronic interstitial nephritis
Statin	Atrovastatin	47(32.87%)	Rhabdomyolysis
	Rosuvastatin	1(0.7%)	
Proton pump inhibitor	Pantoprazole	57 (39.86%)	Acute interstitial nephritis
	Eosemaprazole	2 (1.4%)	
	Lansoprazole	22(15.38%)	
	Rabeprazole	2(1.4%)	
Quinolone	Ciprofloxacin	1(0.7%)	Acute interstitial nephritis, crystal nephrophathy
Cephalosporin	Cefixime	1 (0.7%)	Acute interstitial nephritis
	Cefuroxime	1(0.7%)	
NSAID	Paracetamol	5(3.5%)	Chronic interstitial nephritis

Nephrotoxic drugs

The most commonly prescribed nephrotoxic drugs belong to diuretics and proton pump inhibitors .i.e torsemide and patoprazole respectively shown in Table 6.

DISCUSSION

The polypharmacy and frequency of potential DDIs are high among CKD patients [23]. To identify and categorize drug drug interactions different methods were used. In this study LexiComp is used to predict potential DDIs.

CKD is common in the elderly. The average age of the study population was 54.38 years which is similar to previous study, i.e., 53.81 years and 53.8 by Fasipe O J et al [23] and Busari AA et al [24] respectively. In this study 65.7% men and 34.3% female were suffering from CKD. The gender analysis showed that male patients were more compared to female. Hypertension and diabetes were the most common comorbidities among CKD patients, similar with previous studies [11, 12]. This may be due to the fact that both conditions are the leading causes of CKD worldwide. Depending upon the stage most of the patients fell under stage V (83.2%).Whether or not the disease will progress depends upon the stage and risk factors.

The mean prescribed medications per patient was 6.1% which is similar to the studies conducted by Sgnaolin et al [8] (6.3%) and AI-Ramahi et al [10] (7.87+-2.44) .The studies done by Fasipe O J et al [23] (10.28±3.85) and Diaz G S et al [25] (8.6+-3.4) reported slightly higher values for the mean number of medication received by the patients . All these studies showed that CKD patients were taking multiple drugs. Among CKD patients 66.43% had taking 5-8 drugs per day. Fasipe OJ et al also reported 41.5% patients had 6-10 drugs per prescription [23]. Among 143 CKD, 112 prescriptions had multiple medications which indicate the relatively high frequency of polypharmacy. The deteriorating renal function in CKD patients may lead to many complications like hyperkalemia, metabolic acidosis, volume overload hyperphosphatemia, anemia, hyperlipidemia, and metabolic bone disease and to manage these complications for retarding progression and reducing mortality involves the multiple medications use. Hence polypharmacy becomes more frequent among them [26].

Depending upon the stages of CKD, polypharmacy is more common among advance stage, CKD V (59%). This suggest that the number of prescribed medications increases as the glomerular filtration rate (GFR)declines in advance stage of CKD patients due to worsening of kidney function [23].

The prevalence of pDDIs in this study is 78.3%. A total of 206 pDDIs were identified. The value obtained in the present study is similar with the study conducted by Fasipe O J et al [23]. in West Africa showed 78.0 % of pDDIs prevalence. An another study conducted in South Indian Tertiary Care Hospital by Rama M *et al* showed 76.09 % of pDDIs prevalence [9]. The study conducted by Hegde S et al in India showed 80.8% pDDIs prevalence [12]. All these studies suggest that the prevalence of potential drug- drug interactions among CKD patients is very high and common. The practices of polypharmacy are high among CKD patients [23].The frequency and severity of pDDIs could be affected by the type and number of drugs per patient, because DDI occur when the effects of one drug are changed by the presence of another drug [25, 27].The risk of potential drug interactions increases from 39% to 100% when patients are on more than six medications compared to when they are on 2-3 medications [28].

According to risk rating classification, majority 178 (86.4%) of the interactions were of moderate severity (type C). This is similar to previous studies [10, 23,]. The type X risk rating interaction (avoid

drug combination) was found in one patients only, similar to the study conducted by Fasipe OJ et al [23]. The most frequent DDIs was between oral Calcium carbonate and amlodipine (31.5%%). Result obtained is similar to study done by Al-Ramahi et al [10] but differs from that of Rama et al [9]and Fasipe OJ et al [23]. Rama et al [9] reported ascorbic acid and cyanocobalomin and Fasipe OJ et al [23] reported calcium carbonate and oral ferrous sulphate (9.9%) as most frequent DDIs. Calcium carbonate antagonizes and decreases the vasodialatory effect of amlodipine on the small arteries, thereby reducing the antihypertensive effects.

The multivariate (logistic regression) analysis showed statistically significant association between the number of prescribed medications and the occurrence of DDIs. This implies that as the number of prescribed medications increases, the chance for the occurrence of DDIs also increases. Similar to this result, earlier studies also identified polypharmacy as one of the predictors for the occurrence of potential drug- drug interaction [10, 24, 29]. CKD is a complex disease associated with a number of serious complications and to reduce mortality and morbidity, these complications receive treatment [26].

CKD are important risk factors for increasing vulnerability to nephrotoxic injury. Among 837 prescribed drugs, 277 belongs to nephrotoxic. The types of kidney dysfunction that are induced by nephrotoxic drug include acute tubular necrosis, glomerular and tubulointerstitial injury, haemodynamically mediated damage and obstructive nephropathy Due to the risk associated with using nephrotoxic drug ,prescriber should be prescribed with caution and the dosage recommendations should be strictly followed [29].

CONCLUSION

The prevalence of potential DDIs is high among CKD patients. Polypharmacy has the potential to result a drug-drug interaction. As number of medications increase, the potential for drug interactions also increases Most of these interactions have moderate severity. Prescribers should know all drugs taken by patients including drugs prescribed by other prescribers and all Over the counter drugs, herbal products and nutritional supplement. Medication review is an essential part in the CKD patient.

Nephrologists, Physician, health worker should make use of available interaction detecting softwares to check all prescribed medications for CKD patients so as to identify and avoid the unwanted, undesired and non beneficial drug – drug interactions.

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