



Evaluation of drug induced constipation in CKD patients

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Abstract

Introduction: Constipation is one of the most common gastrointestinal problems among patients with chronic kidney disease (CKD), due to their sedentary lifestyles, poor fiber and fluid intake, concurrent drugs (e.g., phosphate binders) and various co-morbidities (e.g., diabetes). This chronic disorder is commonly thought to be a harmless, self-limiting or treatable disease but its severe, multiple effects have a negative impact on patients' quality of life and can be a significant economic and social burden.

Determining drug-induced constipation is important to know the causality of drug which can be difficult in chronic kidney disease patients who take a variety of drugs, while reducing medications that can trigger constipation is important in the treatment of constipation, it may be challenging in certain patients that have several serious complications.

Materials & Methods: This is an observational/interventional study. The study will be

conducted in the Nephrology Department of KR Hospital, Mysuru. This study was conducted over a period of six months for 33 patients with chronic kidney disease (CKD) who were admitted to the nephrology ward and hemodialysis unit. Patient's demographics data were collected using data collection form and constipation questionnaire (The Patient Assessment of Constipation Symptoms Questionnaire).

Result: Out of 33 patients male patients (78.7%) were predominant while comparing to female patients. More patients (n=20) belonging to age group 46-70 were observed with constipation in increased number because aging contribute to complications in a patient's health condition. PAC-SYM questionnaire showed that majority of patients experienced moderate type of severity of all the symptoms except for rectal burning during or after bowel movement which can be due to the reason they did not suffer from chronic constipation. In our study, severe constipation was only

observed for a patient where he received multiple drugs.

Conclusion: The study was conducted to evaluate drug induced constipation in CKD patients. So it's important to analyze the quality of life of patients receiving these medications in order to control the severe nature of constipation caused by these drugs and find an alternative or less problem causing drugs to increase the quality of life of patients undergoing dialysis.

Keywords: ESKD, CKD, PAC-SYM

Introduction

Chronic kidney disease is defined as abnormalities in kidney structure or function that have been present for three months or longer and have a negative impact on health.¹

Constipation is a condition characterized by bowel symptoms (difficult or infrequent movement of stool, stool hardness, or a sensation of incomplete evacuation) that may occur alone or as a result of another underlying disorder (e.g., Parkinson's disease).²

Chronic constipation (CC) is a common condition that can cause significant morbidity in certain people. Recent meanings of CC have shifted away from a specific focus on stool frequency to a broader concept that aims to encompass all of the symptoms that affected people may experience. As a result, modern treatments aim to not only improve defecation frequency but also to resolve symptoms like bowel comfort, straining, bloating, and distension.³

Constipation is one of the most common gastrointestinal problems among patients with chronic kidney disease (CKD), due to their sedentary lifestyles, poor fiber and fluid intake, concurrent drugs (e.g., phosphate binders) and various co-morbidities (e.g.,

diabetes). This chronic disorder is commonly thought to be a harmless, self-limiting or treatable disease but its severe, multiple effects have a negative impact on patients' quality of life and can be a significant economic and social burden.⁴

Among the various symptoms reported by end stage kidney diseases (ESKD) patients, constipation was listed as the third most common symptom. Constipation has been linked to an increased risk of colorectal cancer, cardiovascular disease, chronic kidney disease, and mortality in recent population- based research. In the case of drug-induced constipation, determining the causality of drug can be difficult in CKD patients who take a variety of drugs, while reducing medications that can trigger constipation is important in the treatment of constipation, it may be challenging in certain patients that have several serious complications.⁵

Therefore this study was conducted with the objective to evaluate drug induced constipation in CKD patients and also about the severity of constipation that followed due to multiple drug administration.

Materials & Methods

Study Design: This was a prospective observational study.

Study duration: This study was carried out for a period of **six months from May 14th 2021- November 14th 2021.**

Study site: This study was conducted in K R Hospital, Mysore.

Source of data and materials:

- Patient data collection form (PAC-SYM)
- Patient medical records
- Patients and patient care taker interview

Study Criteria

Inclusion Criteria

- Patients of age 18 years and above.
- Patients of both genders.
- Patient admitted as inpatient department of Nephrology.
- Patient undergone dialysis.
- Patients who were willing to participate in this study.

Exclusion Criteria

- Patients undergone kidney transplantation
- Patients with cognitive deficits and visual impairment those were unable of answering the questionnaire.
- Patients that had serious illness in an acute treatment phase
- Patients with hyperkalemia.
- Patient who were not willing to participate in the study.

Study procedure

This was an observational/interventional study; the study was conducted in the nephrology department of KR hospital, Mysuru. Considering the inclusion and exclusion criteria, patients were enrolled after taking written consent from each patient for the study. A suitably designed data collection form was used to collect all the necessary information.

Ethical clearance

Institutional Ethical clearance (IEC) was obtained by the Institutional Ethical Committee of Mysore Medical

Table 1: Age Group *Risk Factors of CKD

Gender	Risk Factors	Age Interval		Total
		18-45	46-70	
Female	HTN	2	1	3

College and Research Institute, Mysore before the initiation of the study with certificate No: IN-KA256160552975821.

Result & Discussion

Thirty five CKD patients having end stage renal disease were selected for this study. Among those, 2 subjects did not satisfy the inclusion criteria and were excluded from the study.

Therefore a total of 33 participants were enrolled in for the study.

Gender Distribution

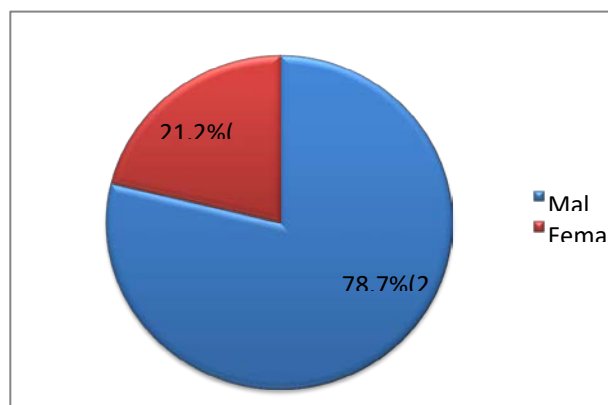


Figure 1: gender distribution in study population

The study participants comprised of 26 males (78.7%) and 7 females (21.2%) with mean age of 48.96 ± 12.26. The details of gender distribution are represented in Figure 1.

Age group with risk factors distribution

More than half of the patients were aged within 46-70 (n=20). Represented in Table 1, patients with CKD had hypertension (n=16) as the most frequently observed risk factor. While only 8 patients had HTN and T2DM which might be the reasons for CKD.

	HTN, T2DM	0	2	2
	NS	1	1	2
	Total	3	4	7
Male	HTN	6	7	13
	HTN, ADPKD	0	1	1
	HTN, T2DM	1	5	6
	HTN, T2DM, COPD	0	2	2
	NS	2	0	2
	T2DM	1	1	2
	Total	10	16	26

Abbreviations: HTN – hypertension, COPD – chronic obstructive pulmonary disorder, T2DM – type 2 diabetes mellitus, ADPKD – autosomal dominant polycystic kidney disorder.

Here more patients (n=20) belonging to age group 46-70 were observed with constipation in increased number because aging contribute to complications in a patient’s health condition.

Distribution of frequency of patients based on symptom in pac-sym scale

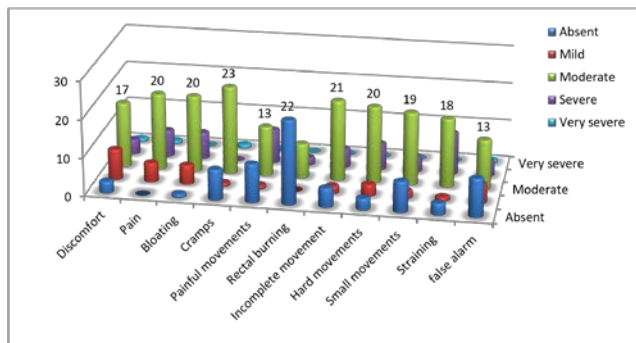


Figure 2: Distribution of Frequency of Patients Based on Symptom in Pac-Sym Scale

The severity of patients constipation were categorized from absent (0) to very severe (4) based on the information provided by the patients. The

questionnaires were asked based on PAC-SYM questionnaire and the distribution of severity is depicted on Figure 2.

Majority of patients experienced moderate type of severity of all the symptoms except for rectal burning during or after bowel movement, where they had no burning sensation. This can be due to the reason they did not suffer from chronic constipation.

Occurrences of constipation caused by drugs along with their Severity

The drugs are categorized based upon their chance of occurrences of constipation into <1%, 110%, >10%, FND and PMS. Individual severities of constipation caused by the drugs are expressed along with the drugs taken by the CKD patients who are demonstrated in Table 2.

Table 2: occurrences of constipation caused by drugs of each group

<1%	1-10%	>10%	Frequency not defined	Post-marketing reports
Ranitidine (1%)	Metoprolol (1%) Rosuastatin (3%) Ranolazine (7%) Nifedipine (2%) Clonidine(10%) Torsemide(2%) Meropenem(4%) Sevelamer (8%) Piperacillin and Tazobactum(5%) Voglibose and Repaglinide(3%) Pantaprazole (4%)	Ondansetron (9%), Tramadol Hydrochloride(35%) andAcetaminophen	Calcitriol Calcium with Vitamin D3 Ferrous sulphate and Folic acid (FS+FA) Phenytoin Lorazepam Ferrous fumarate and Folic acid Cholecalciferol	Azithromycin, Ciprofloxacin, Cyclophosphamide.

Correlation of drugs with severity of constipation

In Table 3 depicted below unfold the frequency of patients receiving the mean of each type of drugs in the

past medication history along with patients severity of constipation.

Table 3: correlation of combination of drugs with severity of constipation

Frequency of Patients	Mean of drugs from each section					Mean of Severity of Constipation
	<1%	1-10%	>10%	FND	PMS	
2	1	3	0	0	0	Mild
4	1	3	0	1	0	Moderate
1	1	2	1	1	0	Mild
8	0	2	0	0	0	Moderate
1	0	4	0	0	1	Severe
8	0	2	0	1	0	Moderate
2	0	3	0	2	1	Moderate
2	0	2	1	0	0	Moderate
1	0	1	1	2	1	Mild
2	0	2	1	1	0	Moderate
1	0	0	0	1	0	Mild

Abbreviations: FND – frequency not defined, PMS – post marketing surveillance. In our study, severe

constipation was only observed for a patient where he received 4 drugs belonging to group of drugs that may

cause constipation in 1-10% of population and a drug from group of drugs undergoing PMS. Even though the occurrence of constipation in the population by drugs in 1-10% is less, the severities of constipation caused by the drugs are severe due to multiple drug administration of drugs belonging to 1-10% group. Among the 33 patients, a patient had no significant treatment plan that could lead to constipation but had constipation of moderate severity that could be due to non-adherence to life style modifications.

Distribution of Common Drugs Causing Constipation

Table 4: Distribution of Common Drugs Causing Constipation

Total Number of Patients	Mean of Severity of Constipation	Most Common Drug Observed (Frequency of Patients)
2	Mild	Torsemide (2), ranitidine (2)
4	Moderate	Ranitidine (4), FS+ FA (4), metoprolol (3), torsemide (3)
1	Mild	FS+ FA, ranitidine, piperacillin and tazobactam
8	Moderate	Nifedipine (5), clonidine (3), pantoprazole (2)
1	Severe	Cyclophosphamide, pantoprazole, piperacillin and tazobactam, clonidine, metoprolol
8	Moderate	FS+FA (4), torsemide (4), ondansetron (4)
2	Moderate	Torsemide (2), ciprofloxacin (2), FS +FA
2	Moderate	Ondansetron (2), pantoprazole (2), tramadol hydrochloride and acetaminophen (1)
1	Mild	FS+FA, ondansetron, pantoprazole, azithromycin
2	Moderate	FS+FA (2), pantoprazole (2), tramadol hydrochloride and acetaminophen (1), Piperacillin and tazobactam (1)
1	Mild	Calcium with vitamin D ₃

By administering these multiple drugs that may cause constipation as a side effect, the severity of the constipation condition could be worsened. In case of ESRD patients due to dialysis, dietary and fluid

In our study according to Table 4 the observed pattern of patient receiving multiple treatments had mild to severe type of constipation in which the most common drugs observed which could be the reason were :

1. In mild – torsemide, ranitidine, FS+FA, ondansetron, pantoprazole
2. In moderate – FS+FA, torsemide, pantoprazole, tramadol hydrochloride and acetaminophen, ondansetron
3. In severe – cyclophosphamide, pantoprazole, piperacillin and tazobactam, clonidine, metoprolol

restrictions, they already contribute towards constipation. So in case of drugs causing severe to mild constipation it's always better to find an alternative

treatment plan to provide the best possible care for the patients to increase their quality of life.

Conclusion

In our study, 33 participants having end stage renal disease were selected in which all patients were undergoing maintenance hemodialysis and this itself is a major factor for constipation. Along with hemodialysis, administration of drugs for the co morbidities the patients are suffering from- contribute towards the increase in severity of constipation. Among both the genders, males were more prone to constipation that could be due to sedentary life styles. The most common co morbidities observed along with CKD are hypertension and diabetes mellitus. Therefore drugs like anti-hypertensive, ant diabetics are extensively used that cause constipation (metoprolol, clonidine, nifedipine, voglibose, torsemide). And other supportive treatments like antibiotics (azithromycin, ciprofloxacin, piperacillin) for patients undergoing surgeries, proton pump inhibitor's (pantoprazole) and H2 receptor receptor blockers (ranitidine) for reducing gastric irritation that are usually caused by antidiabetics. Since more patients belong to geriatric group they are administered with ferrous sulphate + folic acid, calcium with vitamin D3 and ferrous fumarate and folic acid which also contributes towards increase in severity. So it's important to analyze the quality of life of patients receiving these medications in order to control the severe nature of constipation caused by these drugs and find an alternative or less problem causing drugs to increase the quality of life of patients undergoing dialysis.

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