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Pharmacological Management of Complications of End Stage Renal Disease in Patients on Maintenance Hemodialysis.

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ABSTRACT

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End stage renal disease (ESRD) is an important health concern due to the high rates of associated mortality. Complications due to ESRD have been implicated in death or having a significant effect on the patients' quality of life. This study aimed to assess the causes, complications, and the pharmacological management in patients with ESRD who are on maintenance hemodialysis. This prospective observational study included patients visiting the dialysis unit with glomerular filtration rates (GFR) <15 ml/min. Data was collected from case notes, medication charts, dialysis notes and laboratory reports. The complications due to ESRD were classified according to the ICD codes and the management strategies were classified according to the WHO Anatomic Therapeutic Chemical (ATC) code. Among 150 patients enrolled, 112 of them were male patients. The mean age of the study population was 52.51 ± 12.8 years. The most common causes of ESRD were type 2 diabetes mellitus and hypertension. The most common complications associated with ESRD were anemia (93%) and hyperkalemia (92%). Oral iron supplementation and erythropoietin injections were used to manage anemia. Mean hemoglobin levels in patients who received both erythropoietin injection and oral iron, and oral iron only were 8.61 ± 2.16 and 6.3 ± 2.4 respectively. Drugs acting on the alimentary tract (44.8%), cardiovascular system (27.2%) and blood formation (16.8%) were prescribed commonly. Multiple drug use was observed in patients undergoing hemodialysis. Oral iron and erythropoietin injections used together showed improvement in hemoglobin levels as compared to oral iron alone. Patients with co-existing diabetes and hypertension had a higher risk of developing complications with kidney disease.

Keywords: Kidney Disease, End Stage Renal Disease, Hemodialysis

INTRODUCTION

Impairment of normal kidney function often begins with non-specific symptoms such as nausea and vomiting, which progressively worsens with time. When the GFR drops below 15 ml/min, the condition is termed as ESRD. Patients in ESRD require renal replacement therapy, either dialysis or transplantation to remove the uremic toxins and maintain the hemodynamic stability. ESRD is an important health concern because of the costs involved in renal replacement therapies, high rates of associated mortality, and the effect on the patients' quality of life.[1] Over 1.1 million people are estimated to be suffering from ESRD worldwide and an addition of 7% more is further expected each year.[2] In the West, there are over 1 million dialysis patients, with an incidence of a quarter million new patients each year. Amongst these patients, ESRD accounts for nearly 50% of all deaths as a result of its associated complications.[3]

Global burden of disease study estimated that chronic kidney disease (CKD) is ranked 12th among all causes of death (1.4% of all deaths), and is seen to affect men more prominently. Further, CKD is ranked 17th among all causes of disability.[4] In the developed countries, there is a decrease in mortality associated with ESRD as compared to the developing countries. India has a higher prevalence of ESRD due to its marked ethnic diversity. Epidemiological studies conducted in India have shown that the approximate prevalence of ESRD is 860 population per million (ppm) and the approximate incidence of ESRD is 150-200 ppm.[5]

The most important causes resulting in ESRD include diabetes, hypertension and glomerulonephritis.[6] The other causes that can lead to the development of this disease are drug induced kidney damage, interstitial nephritis and the other auto immune disorders. The risk factors that contribute to the progression of ESRD include dyslipidemia, obesity, advancing age, and a relevant family history.[7,8,9,10] Population based studies from India point to diabetic nephropathy as most common cause of ESRD.[5]

Hemodialysis and kidney transplantation (renal replacement therapies) are treatment options recommended for ESRD patients. Despite renal replacement therapies, the prognosis of ESRD remains bleak with an annual mortality rate of dialysis patients (US) being more than 20%.[11] Studies in the Indian population have shown an overall survival period ranging between 14 months and 5 years.[12,13] Among the dialysis treated patients, a mean of 4 co-morbid conditions per

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patient were found and their expected remaining lifespan was shorter by 3 to 11 years as compared to the age matched in the general population.[14]

The complications associated with ESRD represent one of the most important causes of morbidity among the ESRD patients. Management of ESRD requires a holistic approach with dietary monitoring for low salt, protein and fluid intake, and pharmacological interventions for managing of anemia, hypertension, and electrolyte disturbances.[12] The occurrence or progression of ESRD can be delayed based on its etiology. This study was conducted to assess the common etiologies that lead to ESRD, the common complications associated with ESRD, and its management in a tertiary care hospital.

MATERIALS AND METHODS

It was a prospective observational study conducted in nephrology and dialysis units in a tertiary care hospital for a period of 6 months. The study was approved by the Institutional Ethics Committee. Patients with CKD stage-V who underwent dialysis were enrolled in to the study. Patients who were pregnant, who were greater than 80 years of age and who had other serious illnesses & co-morbid factors such as meningitis, cancer, septicaemia were excluded from the study. Informed consents were obtained from all eligible and interested patients. All the relevant and necessary data were collected from the patient's case notes, treatment charts, laboratory reports, notes from the patient or patient's caretaker interviews, and dialysis notes. The patients were followed-up during their respective follow-up visits to the nephrology and dialysis units and relevant information were collected and documented.

Descriptive statistics was used for data analysis. The data obtained was represented as mean ± standard error or mean (SEM) and percentages. The association between the common causes that lead to ESRD and the complications of ESRD were assessed using the descriptive statistical method and chi-square test using the Statistical Package for Social Science (SPSS) Version 17. The etiologies of patients in whom the chi-square value was lesser than 0.05, was determined to have a significant role in development of ESRD.

RESULTS

Out of the patients reviewed (n=150), 74.6% were male and 25.3% were female. The mean age of the study population was found to be 52.51 ± 12.8 years. Patient demographics are depicted in Table 1. Etiologies of ESRD are shown in Figure 1. A total of 1761 drugs were prescribed in the study population belonging to 22 different chemical classes and 8 ATC classes (Tables 2 and 3). All patients received more than three medications. 24% of the patients received five medications. 95% of the patients received six medications and 12.6% of the patients were on four medications.

Table 1: Patient Demography

Total number of patients	**150**
Gender	
Male	112
Female	38
Mean Age of Population (Mean ± SD)	52.51 ± 12.8 years
Mean Serum Creatinine (Mean ± SD)	8 ± 2.64 mg/dl
Mean Serum Haemoglobin (Mean ± SD)	7.8 ± 1.24 g/dL
Mean Serum Calcium (Mean ± SD)	5.7±3.6
Mean Serum Phosphorous (Mean ± SD)	5.5±1.4
Mean Serum Potassium (Mean ± SD)	5.5±1.04
GFR* (Mean ± SD)	10.27 ± 2.80 ml/min
⩾10 ml/min (n)	62
5-10 ml/min (n)	79
⩽5 ml/min (n)	9
Duration of Dialysis	
Twice weekly	133
Thrice weekly	17

*GFR- Glomerular Filtration Rate - Estimated using Cockcroft-Gault equation

Anemia (95.3%), hyperkalemia (92%), hypocalcaemia (69.3%), and hyperphosphatemia (51.3%) were most common complications reported in the study population. For managing anemia, the study population received either erythropoietin or oral iron supplementation, or both. Mean hemoglobin levels in patients who received both erythropoietin injection and oral iron, and only oral iron were 8.61 ± 2.16 and 6.3 ± 2.4 respectively. Hyperkalemia was treated with calcium polystyrene sulphonate (ion exchange resin) and patients with hyperphosphatemia received calcium acetate or phosphate binders such as sevelamer or lanthanum carbonate.

A chi-square test showed significant association between the causes and complications associated with ESRD among the study population, which included those with both type 2 diabetes mellitus and hypertension (p value = 0.032), those with only hypertension (p value = 0.039) and those with only type 2 diabetes mellitus (p value = 0.048) (Table 4).

DISCUSSION

More number of patients with ESRD had both diabetes and hypertension. Data from previous studies show that diabetes, hypertension, estimated GFR (eGFR) <60ml/min/1.73/m^2 and congestive heart failure predict the progression to ESRD.[15] There was more number of males with ESRD in our study population. Though CKD is more common among

Table 2: Most commonly Prescribed drugs in Haemodialysis Patients

ATC CODE	Anatomical Class (Percent of Drugs)	Therapeutic Class	Percentage of patients (n)
A	Drugs affecting Alimentary Tract and Metabolism (44.8)	02 Acid related disorders	6.43 (56)
		04 Antiemetics and anti-nauseatives	1.03 (9)
		05 Drug used in diabetics	7.12 (62)
		06 Laxatives	0.91 (08)
		11 Vitamins	12.64 (110)
		12 Mineral supplements	16.67 (145)
B	Blood and blood forming agents (16.8)	01 Antiplatelets	0.45 (04)
		03 Anti-anemic preparations	16.43 (143)
		02 Antihypertensive	0.80 (07)
C	Cardiovascular system (27.2)	03 Diuretics	7.01 (61)
		07 Beta blocking agents	3.67 (32)
		08 Calcium Channel blockers	7.35 (64)
		09 Agents acting on renin angiotensin system	3.56 (31)
		10 Lipid modifying agents	4.82 (42)
J	Anti infective for systemic use (3.56)	01 Anti-bacterials for systemic use	3.56 (31)
N	Nervous system (2.52)	02 Analgesics	2.52 (22)

Table 3: Other Less Commonly Prescribed Drugs

ATC CODE	Anatomical Class (Percent of Drugs)	Therapeutic Class	Percentage of patients (n)
H	Systemic hormonal preparations (1.60)	01 Corticosteroid for systemic use	1.03 (09)
		02 Thyroid therapy	0.57 (05)
M	Musculoskeletal system (0.45)Respiratory	01 Anti inflammatory and anti rheumatic products	0.45 (04)
R	System (1.86)	03 Drugs for obstructive air way diseases	0.57 (05)
		05 Cough and cold preparation	1.03 (09)
		06 Anti histamines for systemic use	1.26 (11)

women regardless of age, men are 50 times more likely to progress to kidney failure than women.[16,17] However, the male:female ratio among our dialysis patients does not reflect an increased incidence of ESRD in men. Other factors that may contribute to increased incidence or progression to ESRD such as differences in etiology, socioeconomic conditions, lifestyles of men and women need to be investigated further. Also most patients undergoing hemodialysis belonged to ages between 55 and 65 years, whereas it was noted that the cut-off age in the developed countries was 65 years.[15]

Our patient population had diabetes, hypertension, and glomerulonephritis as the most common etiologies of ESRD. These findings were similar with data reported from a previous study in India[18], although glomerulonephritits was the leading cause in that study. Data from US show that most common causes for incident ESRD are diabetes mellitus, hypertension, glomerulonephritis and polycystic kidney disease (USRDS Annual Data Report 2012, available from www.usrds.org) .

Most patients in our study underwent hemodialysis twice a week. The NKF-KDOQI recommends that the frequency of dialysis can be maintained anywhere between 2−6 times per week. However as the disease progresses, a twice-weekly hemodialysis may not be appropriate. Duration and frequency of dialysis for patients with residual native kidney urea clearance (Kr) <2ml/min/1.73m^2 is decided based on their Kt/V (fractional clearance of urea).[19] It has been postulated that frequent dialysis mimics physiological clearance of solutes and water and improves the outcomes in these patients. But randomized controlled trials led to the conclusion that increasing the frequency of dialysis to three times weekly patients did not improve patient outcomes.[20] Patient willingness and affordability for frequent dialysis is an important concern during management of ESRD with hemodialysis.

The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are hyperglycemia (causing hyperfiltration and renal injury), advanced glycosylation products, and activation of cytokines. Hyperglycemia

Table 4: Association between causes of ESRD and its complications

Cause	Chi^2	Odds ratio	P value
DM + HTN	9.47	22.5 (1.66-305.73)	0.032*
HTN	8.36	20.0 (1.47-272.31)	0.039*
DM	5.514	12.60 (1.07-148.1)	0.048*
Glomerulonephritis (GN)	2.48	7.0 (0.050-98.60)	0.184
HTN + GN	2.1	6.0 (0.45-74.78)	0.197
Interstitial nephritis	1.94	5.4 (0.43-66.68)	0.206
Auto immune disease	0.72	3.0 (0.28-39.7)	0.40

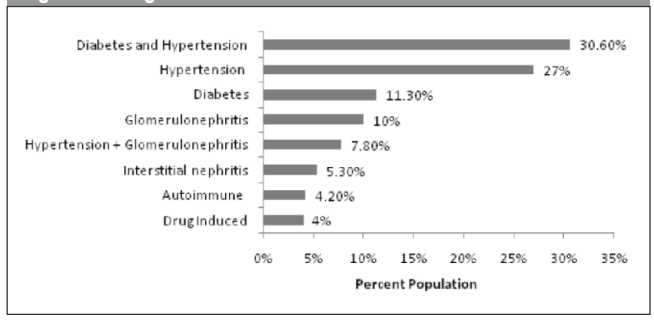
(Drug-induced ESRD taken as reference) * Significant at ($p \leqslant 0.05$) by chi-square.

increases the expression of transforming growth factor-beta (TGF-β) in the glomeruli and of the matrix proteins specifically stimulated by this cytokine. TGF-β may contribute to cellular hypertrophy and enhanced collagen synthesis observed in persons with diabetic nephropathy. Hyperglycemia also may activate protein kinase C, which may contribute to renal disease and other vascular complications of diabetes.[4]

The most common complications were found to be anemia of chronic disease and electrolyte imbalances such as hyperkalemia and hypophosphatemia. Out of 150 patients enrolled into the study, 143 (95.3%) patients were found to have anemia (Hb ⩽ 8g/dl) and the mean hemoglobin value in the study population was 7.8. Normochromic normocytic anemia due to decreased renal synthesis of erythropoietin starts early in the course of disease and becomes more severe as the GFR progressively decreases with the availability of less viable renal mass. RBC survival is decreased, and tendency of bleeding is increased due to uremia-induced platelet dysfunction. Other causes of anemia in chronic kidney disease include chronic blood loss during dialysis, secondary hyperparathyroidism, inflammation, nutritional deficiency, and accumulation of the inhibitors of erythropoiesis.[21]

The patients who are receiving both oral iron therapy and erythropoietin injection were found to have improved mean hemoglobin levels (8.61 ± 2.16) as compared to those who were receiving either oral iron therapy (6.3 ± 2.4) or erythropoietin injection (7.4 ± 1.12). The KDOQI guidelines for the management of anemia recommend supplemental iron along with erythropoietin injections in patients undergoing hemodialysis; but there is lack of evidence regarding iron targets in this population. Also, there is insufficient information regarding the efficacy of oral versus intravenous iron therapy.[22] Our study was not designed to make such a comparison, however such data would be useful for clinical practice recommendations.

Fig. 1: Etiologies of ESRD



The average number of drugs per patient in this study was found to be 5.5. However, according to a study conducted at University of The Ryukyus, Japan that analyzed the drug prescriptions in chronic hemodialysis patients, the average number of drugs per patient was found to be 7.2.[23] Among the various ATC classes of drugs used in the nephrology unit, drugs affecting the alimentary tract and metabolism were commonly prescribed, followed by cardiovascular system which included antihypertensives and dyslipidemic drugs. Among the blood forming agents, iron and multivitamins with folic acid were most commonly prescribed.

Due to lack of a control group, the association between the causes of ESRD and its complications was assessed by considering patients with drug induced ESRD as reference since this group had the least number of complications among study patients. Those patients who had both diabetes and hypertension were found to have 23-fold higher risk of developing complications such as anemia and electrolyte imbalance. Patients who were having only hypertension had a 20-fold higher risk while those with only type 2 diabetes mellitus has a 12-fold higher risk of developing complications as compared to patients with drug induced ESRD.

CONCLUSION

Type 2 diabetes mellitus, hypertension, and glomerulonephritis are the most common causes of ESRD. Targeting diabetic and hypertensive patients for better control of their disease may limit the development of kidney disease or delay its progression to ESRD. Anemia and electrolyte imbalances were the most common complications reported. Oral iron supplementation and erythropoietin injections when given together resulted in improved serum hemoglobin levels.

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