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Transfusion Support in Chronic Kidney Disease Patients undergoing Maintenance Hemodialysis

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ABSTRACT:
INTRODUCTION:
Anemia is highly prevalent in end stage renal disease patients and inadequate renal erythropoietin production is a contributing cause for anemia. With the help of alternative therapies like iron therapy and recombinant erythropoietin therapy, goal of optimal hemoglobin concentration is being maintained. Blood transfusions are deemed necessary in chronic anemia patients with inadequate tissue oxygenation or cardiac failure. Decision making by clinician for blood transfusions depends on various factors which need to be analyzed. In our study, these factors are analyzed and practice guidelines are formed.
MATERIALS AND METHODS:
50 CKD patients undergoing maintenance hemodialysis are studied over a period of 2 years. Clinical history, signs and symptoms,iron therapy and ESA therapy, pre transfusion hemoglobin trigger, type of blood component and transfusion history of these patients data is collected and analyzed with calculating transfusion rates in different categories.
RESULTS:
All patients are categorized into 2 categories based on the pre transfusion hb levels, with <7gm% in category 1 and >7gm% in category 2. Transfusion rate is higher in the category where hb is <7gm/dl, male patients, presence of comorbid conditions and those patients who are not receiving iron therapy and ESA agents
CONCLUSION:
In dialysis patients, with CKD, blood transfusions should be advised judiciously because of the various risks associated with it. Clinician decision is largely based on the risk benefit analysis of transfusion and needs to be analyzed.

I. INTRODUCTION:

Chronic kidney disease (CKD) is defined as the presence of either kidney damage or glomerular filtration rate GFR < 60 ml/min/1.73m2 for more than 3 months. It is also defined by pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies [1]. A common complication in moderate-to-severe CKD is anemia, which is largely due to declining endogenous erythropoietin production by the damaged kidneys [2-5]. It can also be caused by inflammatory cytokines (C-reactive protein, interleukin-6), absolute iron deficiency, vitamin B12 or folic acid deficiency and decreased marrow response to erythropoietin [6].

Anemia is associated with an increase in mortality and morbidity of patients with CKD. Symptoms include anorexia, fatigue, decreased cognition and mental acuity, sleep disturbances, increased risk of hospitalization and prolonged hospital length of stay, left ventricular hypertrophy and congestive heart failure [7]. Initially treating physicians used iron tablets and anabolic steroids as treatment options to improve the hemoglobin levels. Blood transfusions were reserved only when other methods failed to improve Hb or if symptoms persisted in spite of it [8].

Identification and cloning of human erythropoietin gene led to production of recombinant human erythropoietin (EPO), which was approved by Food and Drug administration (FDA) in 1989, led to dramatic improvement in hemoglobin levels and anemia symptoms in CKD patients [9]. Erythropoietin stimulating agents (ESA) can be administered either intravenously (IV) or subcutaneously (SC) once a week or less frequently. Most commonly used ESAs are Epoietin Alfa and Darbepoietin Alfa, the latter having 3-fold longer half-life and greater biological activity [10]. ESAs have alleviated the need for blood transfusions in dialysis patients and also changed attitudes towards blood transfusion usage among treating physicians [11].

In India, there is a significant burden of CKD, although exact figures vary [5]. Lack of access to health care services, especially in the rural areas prevents diagnosis of CKD [3]. The Indian CKD registry was set up by the Indian society of nephrology in 2005 with the aim to serve as a comprehensive nationwide data warehouse for studying various aspects of CKD [3]. Due to cost constraints, some patients who are unable to afford ESA agents and some patients with hypo responsiveness to ESA agents have become one of the major causes for severe anemia. This eventually led to opting for blood transfusion for treating

anemia and its symptoms in CKD patients. Blood transfusions are avoided when possible and are considered only when benefits outweigh the risks and if other treatment options are ineffective. If chronic kidney disease patients are eligible for solid organ transplantation, transfusions are avoided to minimize the risk of alloimmunization [12].

In our study, treatment options for CKD patients include iron tablets or injections IV or IM, ESA agents and blood transfusions. The transfusion trigger in CKD patients, on maintenance hemodialysis, may vary according to different studies. In many studies, transfusion trigger is Hb<7gm/dl and it also depends on the symptoms and signs caused by anemia [10]. In our study, we evaluate the need and factors which are affecting the decision making of clinicians for opting blood transfusion in chronic kidney disease patients on maintenance hemodialysis.

II. AIMS & OBJECTIVES:

This study evaluates the pre-transfusion trigger, indication for blood transfusion and type of components transfused for CKD patients. Analyzing transfusion rates in different groups helps in predicting the transfusion decision making of CKD patients.

III. MATERIALS & METHODS:

The source of data is collected from patients admitted in the dialysis unit of Nephrology Department of Kamineni Institute of Medical Sciences, Narketpally during a study period of 2 years from October 2015 to September 2017.

A total of 66 chronic kidney disease patients undergoing maintenance hemodialysis (HD), who are registered cases in the dialysis unit are selected by simple random technique. The criteria for selecting cases for study include various parameters which satisfy the objectives of the study and fulfill inclusion and exclusion criteria. Out of 60 patients, 50 are selected based on the inclusion criteria which include adults >18 years of age with chronic hemodialysis with a frequency of minimum once a week of HD.16 patients were excluded from the study based on exclusion criteria i.e. patients with acute renal failure, who are undergoing peritoneal dialysis, presence of malignancy, undergoing treatment with cytotoxic drugs or steroids

Study protocol is approved by institutional ethics committee where a detailed informed consent regarding the aims, objectives, methods, advantages and adverse effects is signed and filed in patient's case sheet. Retrospective data of 6 months was collected from all the patients on maintenance hemodialysis by reviewing their case sheets and follow up is done for up to 24 months.

All the patients are categorized into 2 categories based on the absolute pre transfusion hemoglobin level as category 1 with hemoglobin less than 7gm/dl and category 2 with hemoglobin level more than 7gm/dl. This is a prospective study where data is collected on clinical history, physical examination findings, laboratory investigations, IV iron and ESA injections prescriptions and transfusion history which means evaluating indication for transfusion, pre transfusion hemoglobin trigger levels, prescriber, type of blood component and number of transfusions given to each patient during the study period.

The data was analyzed using MS excel software. Frequency, Percentage, row percentage and column percentage for each variable were calculated and 95% confidence intervals were taken to define normal range.

IV. RESULTS:

50 patients are registered into the study based on the inclusion criteria. A total of 46 patients completed the 24 months study period. Remaining 4 died during the study. All patients are distributed into 2 categories based on their pre transfusion Hb value. 1st category has Hb <7gm% and 2nd category has Hb >7gm%. Data of these 2 categories is summarized in table 1.

Mean age group is 52.32 ± 10.4 years with male preponderance (62%) is seen in the present study. 42 CKD patients (84%) are associated with comorbid conditions (diabetes mellitus, hypertension). Hypertension (64%) being the commonest comorbid condition than Diabetes Mellitus (20%) in the present study.

Treatment given to the CKD patients comprise of IV iron injections, erythropoietin stimulating agents (ESA) agents and blood transfusions. Only 30% of patients received intravenous iron injections based on their affordability. 100% patients received ESA injections once a week as a part of free treatment scheme by the Government of India.

Out of total 50, 6 patients did not receive any transfusions, 18 patients received at least 1 unit of blood, and 26 patients received more than 1 unit of blood. There were a total of 160 units of blood transfused during the 2 year follow up period with an overall transfusion rate of 3.2%. Whole blood is the most commonly used blood component in the study cases i.e.105 units (65.6%) than packed red blood cells (PRBC) as seen in table 2. Majority of the blood components transfused were B Rh

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positive (40.6%) followed by O Rh positive (38.1%)

Maximum transfusions (85%) were ordered by nephrologists with critical care physicians ordering for 15%. About 80% of transfusions were done in dialysis unit while 20% occurred in an inpatient setting. The most common indication for transfusion was low hb value (94%) 47/50. Fatigue, breathlessness and other cardiovascular symptoms comprise 6% of indications. 3/50.

All patients were grouped into 2 categories based on their mean pre-transfusion hemoglobin value. Hemoglobin value less than 7gm% and hemoglobin value more than 7gm%. 21 patients (42%) out of 50 had hemoglobin value <7gm/dl. Remaining 29 patients (58%) had hemoglobin level>7gm/dL. Maximum number of transfusions are given to hemoglobin level of <7gm/dl i.e. 127 units (80%) which comprise only 42% of the patients. Remaining 20% of transfusions i.e., 33 units of blood are issued to the patients belonging to the category of hemoglobin >7gm/dL. 80% of transfusions are by whole blood and remaining 20% are packed red blood cells as seen in table 2.

Transfusion rate is higher in the category where hb is <7gm/dl, male patients, presence of comorbid conditions and those patients who are not receiving iron therapy and ESA agents.

Table 1: Baseline characteristics of CKD patients

BASELINE CHARACHTERISTICS	HB< 7GM/DL n=21	HB>7GM/DL n=29
Age(years):		
20-40	3	3
41-60	12	23
61-80	6	3
Males	15	16
Females	6	13
Median hb (gm/dl)	6.5	8.3
Comorbid condition:		
Diabetes	3	7
Hypertension	14	18
Glomerulonephritis	4	4
Vascular access:		
AV fistula	18	24
Catheter	0	0
Graft	3	5
Treatment options:		
ESA injections	21	29
IV iron injections	4	11
Outpatient setting	16	28
Inpatient setting	5	1
Prescriber		
Nephrologist	16	28
Critical care physician	5	1
Transfusion history:		
Indication for transfusion/ Number of transfusions	Low hb/ 127(80%)	Symptoms of anemia/ 33(20%)
Type of component:		
Whole blood	78	27
Packed RBC	49	6
Commonest blood group	B RH POSITIVE	O RH POSITIVE

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Table 2: Transfusion support for different levels of hemoglobin concentration:

Hemoglobin range	Whole blood (%)	Packed RBC (%)	Total (%)
<7.0gm/dl (%)	78(74)	49(89)	127(80)
>7.1gm/dl (%)	27(26)	6(11)	33(20)
TOTAL (%)	105(100)	55(100)	160(100)

V. DISCUSSION:

Anemia is major complication of CKD that is associated with lethargy, weakness, shortness of breath, exercise intolerance, reduced health-related quality of life and decreased survival rate [1-4]. Anemia management in CKD patients depends on the severity of the disease and clinical symptoms of the patient. It is done by IV iron injections, ESA agents and blood transfusions [5].

Prior to the introduction of recombinant human erythropoietin (EPO), red blood cell (RBC) transfusions were frequently required when iron and anabolic steroids failed to improve the clinical symptoms of anemia associated with hemoglobin (Hb) levels that were commonly less than 7 g/dL. After the approval of EPO in the US in 1989, the Hb levels of patients on hemodialysis dramatically improved and the need for RBC transfusions decreased significantly. In 2011, FDA issued a black box about potential risks with ESA therapy to Hb>11 g/dL while recommending that there is no safe hemoglobin target level, or ESA dose [8].

In 2012, the National Kidney Foundation and the Kidney Disease Improving Global Outcomes (KDIGO) Foundation launched a new set of guidelines regarding anemia management, recommending avoidance of RBC transfusions to minimize the risk of allo-sensitization in patients eligible for organ transplants [2]. KDIGO guidelines suggests consideration of RBC transfusions in cases where ESA therapy is ineffective and patients have cancer or cancer history. The guidelines emphasize that Hb threshold alone should not be used to decide whether to transfuse or not [2,4]. The need for RBC transfusion should be reserved for patients who require an immediate increase in their RBC mass due to symptomatic anemia [8]. AABB-2016 guidelines [13] recommend RBC transfusion for hemodynamically stable adult inpatients or ICU patients if Hb≤7 gm/dl. Globally, anemia management guidelines for CKD patient recommend maintaining hemoglobin levels to 10 to 10.5g/dl, and using lowest possible ESA dosages to avoid the need for red blood cell transfusions [14].

In our study, we performed an analysis on the transfusion decision making for CKD patients undergoing maintenance hemodialysis. In many such studies, prevalence of blood transfusions are calculated as transfusion rate per patient years and odds ratio for probability of transfusion. Firstly, pre transfusion absolute Hb level of < 7gm/dl is taken as transfusion trigger. In our study, 80% of transfusions are given to the patients with pre transfusion hemoglobin level <7gm/dl, which is similar to Whitman et.al. [15] Where majority of transfusions are given if Hb is less than 7.5gm/dl. Elizabeth v Lawler et.al14 studied 97,636 CKD patients with 16% increased risk of transfusion in category of Hb<7gm/dl. This emphasizes that absolute pre-transfusion Hb value is the decision maker in CKD patients in many studies.

Transfusions to category of Hb>7gm/dl are mainly dependent upon the complexity of medical diagnosis, anemia symptoms and comorbid conditions. Nephrologists considered other treatment options like IV iron injections and ESA agents for treating anemia. They limited transfusions for Hb >10gm/dl keeping in view of iron overload and transfusion related adverse events [2].

Secondly, transfusion rate is seen to be higher in patients with comorbidities, male patients and in patients without IV iron treatment. In our study, mean age group was 52.3 ± 10.4 years where majority are males (62%). Similarly, a study by Mohan M Rajapurkar et.al [3] documented mean age of CKD patients as 50.1 ± 14.6 years and 70% of patients are males. Singh A.K et.al. [16] studied CKD patients with mean age of CKD patients as 45.2 ± 15.2 years with male preponderance (55.1%). Whereas Y.J. Anupama and G. uma [5] in their study, documented mean age as 39.8 ± 15.87 years with female preponderance (54.43%).

Comorbid conditions such as diabetes mellitus, hypertension, and glomerulonephritis have a profound effect on the severity of CKD, patient functional status and stability of the Hb level. In the present study of 50 cases, diabetic mellitus is seen in 10 cases (20%) and hypertension in 32 cases (64%) as comorbid conditions. Many studies has shown hypertension as the most common comorbid condition in CKD patients contributing as the factor for severity of illness and transfusion decision making. Transfusion rate in patients with comorbid conditions is higher with 84% of transfusion events in our study. Similarly, Agarwal and Srivastava [4] documented comorbid

conditions in 4972 CKD patients in New Delhi, with 31.37% patients showing hypertension and 4.19% patients showing diabetes in their study. Singh N.P. et.al [17] documented hypertension in 31.2% patients and diabetes in 7.3% patients of chronic kidney disease in a sample size of 5252. P.P Varma et al [18] in their study from rural belt of Karnataka stated prevalence of 15% hypertension and 1.53% diabetes in their study of CKD patients with a sample size of 3398. Whereas Mohan M Rajapurkar et.al documented his study in Indian CKD registry consisting diabetic nephropathy as a predominant cause of CKD in India. Indian CKD registry has documented hypertensive Nephrosclerosis in 12.9% and diabetic nephropathy in 31.3% cases as the cause of CKD [3].

During the last 30 years, packed red blood cells have been most often used for blood transfusion. Whole blood transfusions are associated with more febrile non-hemolytic reactions, volume overload, allo-sensitization hazards than packed red blood cells [19]. Packed RBC were introduced to reduce the immunization hazards of whole blood and to preserve leukocyte rich and thrombocyte rich blood products for more targeted use for people lacking these components [20]. In present study, whole blood transfusions rate (65%) is comparatively higher than PRBC transfusion rate (35%). This choice of preference for whole blood should be changed with proper education and guidelines for transfusion. A study by Robert N Foley et al [21] showed more packed RBC transfusions (92.5%) than whole blood transfusions (7.5%) in CKD patients.

VI. CONCLUSIONS:

Large efforts have been made to develop practice guidelines for management of CKD patients with different treatment options, but much is still to be done to encourage implementation of these guidelines. Decision making regarding blood transfusions is clinically complex, variable and unpredictable. Hemoglobin level, functional status and comorbid conditions strongly influenced the decision making in our study. To ensure real improvement in health care outcomes, more emphasis should be placed on implementation strategies of blood transfusions, including the development of local support systems, clinical audit programs, and analyzing the feedback information concerning current practices. This may help in decreasing the morbidity and mortality and pave for a better quality of life for CKD patients.

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