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Commentary

The Conundrum of Managing Anemia in Chronic Kidney Disease Patients on Dialysis with Associated Hemoglobinopathies- Perspective from a Single Nephrology Centre in North –Eastern India

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Anemia is a common complication in chronic kidney disease (CKD) and has been associated with a reduced quality of life [1] as well as worse survival [2] and increased morbidity and mortality [3]. The prevalence of anemia is more severe as the estimated glomerular filtration rate (eGFR) declines and is 8.4% at stage 1 to 53.4% at stage 5. Similar data is observed in a more recent paper by the CKD Prognosis Consortium which also observed an increased prevalence of anemia among diabetic patients, independent of eGFR and albuminuria [4]. In CKD patients, EPO deficiency starts early in the course of CKD and appears initially, when eGFR falls below 30ml/min/1.73m2, this deficiency becomes more severe [5]. This absolute EPO deficiency can be caused by a decrease EPO production and /or errors in EPO sensing. CKD produces an alteration in oxygen delivery to the kidneys and results in adaptation of renal tissue to consume less oxygen and subsequent maintenance of normal tissue oxygen gradient. As a consequence, prolyl-hydroxylase domain (PHD) enzymes which regulates HIF activity remain active, the HIF heterodimer is not formed and the EPO gene is not activated [6]. Some CKD patients may also present with a functional EPO deficiency or EPO resistance, where normal range. EPO levels co-exist with low hemoglobin levels indicating a blunted bone marrow response to endogenous and exogenous EPO. Mechanisms hypothesized for EPO resistance include presence of pro-inflammatory cytokines thought to induce apoptosis and down regulation of expression of EPO receptor.

In addition to EPO deficiency, anemia may also be due to factors such as associated hemoglobinopathies, blood loss and iron/folate, B12 deficiencies. Hemoglobinopathies constitute an imperative causative factor for anemia in childhood and adults. This cause may be especially observed in those regions where the prevalence of hemoglobinopathies are seen in a higher frequency. The common hemoglobinopathies, as per a World Health Organization (WHO) 1972 report includes hemoglobin S(Hb S), hemoglobin C (Hb C) , hemoglobin D (Punjab) and hemoglobin E(HbE) . Beta thalassemia is prevalent throught the world with variable frequency. A broad spectrum of diverse ethnic groups has a high prevalence of abnormal hemoglobin and thalassemia. The incidence of Hb E from various population survey of Assam from 23% to 78% [8]. Hb E was first discovered in 1954 in a person of Guatemalan origin with Spanish and Hindu ancestry and is the 4th abnormal hemoglobin variant discovered after Hb S, Hb C and Hb D2 [10]. Hb E is a β chain mutant hemoglobin which glutamic acid B 26 is substituted by lysine. Hb E disorders are the most prevalent hemoglobinopathies in South East Asia and of the estimated 30 million persons with Hb E disorders, more than 80% live on the South East Asian mainland. In India, Assam and the neighboring states have been identified as a region where the prevalence of Hb E is high. In a largest study of its kind looking at the prevalence of hemoglobinopathies in Assam done by Baruah et al [13], out of 9000 patients, abnormal hemoglobin fraction were seen in 60% of patients(5320) . Of these Hb E gene was detected in 4315 patients, of which Hb E trait was seen in 2214 followed by Hb E disease in 1892 patients. The high incidence of hemoglobinopathies is unique for this part of the country. It has been well established that the incidence of Hb E gene in North-eastern India is one of the highest in the world. This is because of the migration of various races over the ages and hence being home to an assortment of socio-cultural, linguistic and ethnically diverse group of people.

Dialysis patients with associated hemoglobinopathies present a unique challenge on hemodialysis since presentation with moderate to severe anemia is not unknown. The exact incidence of hemoglobin disorders on dialysis patients is not clear, though this association may be seen with greater frequency in regions of the world with increased prevalence of hemoglobinopathies in the local population. In β thalassemia, where EPO

levels are low relative to degree of anemia, EPO treatment improves anemia state. Since RBC and platelets of these patients are under oxidative stress, the role of EPO as an antioxidant has been evaluated [12]. RBC and platelets from patients with β-thalssemia demonstrates a reduced glutathione (GSH) content than their normal counterparts. Membrane lipid peroxidation and hence shortening of life span of RBC has been found to be ameliorated by EPO. In this regard, it is important also to note that EPO requirements may be higher in CKD patients with pre-existing hemoglobinopathies. The efficacy of EPO in dialysis patients with β-thalassemia minor has beenstudied by DiIorio et al [14, 15]. The presence of thalassemia minor causes EPO resistance and more serious anemia. In the above mentioned studies, EPO requirements varied from 200.3±94.3/kg/week at the start to 407.0± 130.5 U/kg/week at 12 months. It is evident that very high doses of EPO may be necessary to correct anemia in this group of patients. Doses as high as 60,000 units /week may be necessary and may not produce side effects if correction is done gradually. However it is important to note that other factors such as iron overload or deficiency, hyperparathyroidism or aluminium intoxication may also be responsible for EPO resistance. Nutritional anemia is also responsible for the wide prevalence of anemia in the local population and nutritional factors causing anemia cannot be ignored.

Our own preliminary study (unpublished data) looking at EPO requirements in our newly established dialysis centre involving about 15 ESRD patients who were on twice weekly hemodialysis subsidized by the Central Govt schemes has revealed predialysis hemoglobin average of 6.4 g/dl ±1.68g/dl. We have not been able to do hemoglobin electrophoresis in any of these patients due to financial difficulties and inability to get tests done by the patients in our centre. EPO requirements varied widely from 75.6±30.5U/kg/week to 200.4±25U/kg/week to maintain hemoglobin above 8-9g/dl. The majority of patients (66.7%) had hemoglobin levels between 6.5-7.2gm/dl.

In conclusion, we would like to bring to attention that associated hemoglobinopathies along with anemia of CKD presents with more severe anemia, the management of which may require much higher than conventionally used doses of EPO. Unresponsiveness to conventional doses of EPO will require awareness and screening to pick up abnormal Hb variants in geographically prone areas. It is important for the treating nephrologist to bear this in mind. More research is clearly needed on this topic.

Conflict of Interest: None declared

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