

Management of Anemia in CKD: A Review

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Abstract: Chronic Kidney Disease leads to progressive failure to the kidney. If untreated, a number of complications may arise such as anemia, hyperlipidemia, cardiovascular disease. Renal anemia is highly prevalent in CKD patients (both in dialysis and nondialysis). Anemia can be managed by using either Erythropoietin Stimulating Agent (ESA) or by IV iron therapy. Recombinant human erythropoietin (rHuEPO) is widely used ESA to treat anemia. Hemoglobin (Hb) variation can be controlled by using these agents. The IV iron therapy is also considered a standard care in anemia management because it can reduce the exposure to ESA. Anemia contributes to increases morbidity, mortality and poor quality of life. Treating anemia mainly in dialysis patients with ESA reduces the risk of blood transfusion and increase the patient quality of life. This is because it can cause either hyporesponsiveness or erythropoietin resistance. Another recently discovered drug Roxadustat is a promising therapeutic approach against anemia in CKD. The hemoglobin response of roxadustat is independent of inflammatory microenvironment.

Key words: Chronic kidney disease, anemia, erythropoietin, hemoglobin, erythropoietin resistance, Roxadustat

I. INTRODUCTION

Kidney disease is defined as a heterogeneous group of disorders which affects the kidney structure and function. Duration of less than 3 months is defined as acute and duration of greater than 3 months or is termed as chronic. Chronic kidney disease is a slow and progressive loss of kidney function over a period of several years. Eventually, a person will develop permanent kidney failure. Chronic kidney disease, also known as chronic renal failure, chronic renal disease, or chronic kidney failure. As kidney failure advances and the organ's function is severely impaired, dangerous levels of waste and fluid can rapidly build up in the body. Treatment is aimed at stopping or slowing down the progression of the disease - this is usually done by controlling its underlying cause. Common symptoms include blood in urine, high blood pressure, and fatigue. Causes include diabetes and specific kidney diseases, which consist of polycystic kidney disease. There is no cure for chronic kidney disease, which means treatment is focused on reducing symptoms. Diagnosis commonly occurs after blood tests, kidney scans, or biopsy. Assessment of CKD severity can be facilitated by using National Kidney Foundation developed criteria, as part of its Kidney Disease Outcomes Quality Initiative [1].

II. COMPLICATIONS OF CKD

2.1 CKD Associated Anemia: Anemia is defined as the reduction in the red blood cell measurement mainly in Hb

concentration, hematocrit or RBC count. WHO defines anemia as Hb less than 13g/dL in men and post-menopausal women and less than 12g/dL in premenopausal women. The National Kidney Foundation defines anemia as, hemoglobin less than 13.5g/dL in men and less than 12.0g/dL in women [2]. Anemia in CKD results from several mechanisms includes Iron, folate and vitamin B12 deficiency, GI bleeding, severe hyperparathyroidism, systemic inflammation, shortened RBC survival. Reduced erythropoietin synthesis is most important etiology.

- 2.2 CKD Associated Mineral and Bone Disorders:** Abnormalities in bone and mineral metabolism and extraskelatal calcification is one of the complication associated with CKD. Primary site for phosphate excretion and hydroxylation of vitamin D is the kidney. CKD patients develops hyperphosphatemia because of impaired kidney function. This causes the serum calcium level to fall resulting in increased secretion of parathyroid hormone. In stage 3 of CKD rising in phosphorous level can be found. Mortality in CKD patients is significantly increased in bone mineral disorder. The treatment begin with restricts dietary phosphorous intake, phosphate binders also used.
- 2.3 Cardiovascular Risk:** Cardiovascular risk is increased in end stage renal disease mainly in dialysis patients. Hypertension is one of the major risk factor that associated with CKD. Anemia and hypertension play a role in the development of LVH. Inflammation also play a role in mediating CV risk in CKD found in renal impairment patient with or without diabetes and hypertension.
- 2.4 Dyslipidemia:** It is one of the major risk factor for CV morbidity and mortality. As renal function declines, prevalence of hyperlipidemia increases.
- 2.5 Nutritional Issues:** In CKD patients the nutritional requirements are altered and metabolism of protein, water, salt, potassium and phosphorous are affected. In CKD patients, nutritional disorders may found which is contributed to the both inadequate nutrient intake and ineffective nutrient utilization. In patients with chronic renal impairment the nutritional health in patients can be preserved by maintenance of neutral nitrogen balance Treatment goals include maintain optimum nutritional status and establishing a nutritional plan that is acceptable to the patient. To assess nutritional status, several nutritional markers can be used [3].

Risk factors includes hypertension, diabetes, dyslipidemia, life style factors: tobacco, family history, aging, low birth weight, maternal diabetes mellitus. Hospitalizations are very frequent in ESRD patients who are under the treatment of dialysis. By reducing repeat hospitalization quality of life can increase.

III. MECHANISM OF ANEMIA IN CKD

Renal anemia described as normocytic, normochromic and hypoproliferative. The etiology of anemia in CKD mainly includes EPO deficiency, abnormal iron metabolism, oxidative stress, reduced erythrocyte survival duration, blood loss, chronic inflammation, nutritional deficits. Peritubular interstitial fibroblast like cells which is the Renal Erythropoietin Producing Cell (RPC) are the major source of erythropoietin in kidney. Dysfunction of RPC leads to loss of ability to synthesis EPO, resulting in erythropoietin deficiency and renal anemia development. Additionally, majority of myofibroblast were derived from RPCs, which is correlated with hematocrit, renal EPO mRNA renal fibrosis. Negative iron balance contributes to the renal anemia, apart from the erythropoietin deficiency. This is characterized by impaired iron release from body stores, resulting in renal anemia which is manifested by low transferrin saturation and high ferritin. Excess of hepcidin imbalance the iron hemostasis in CKD patients. Hepcidin can maintain systemic iron balance via regulating the ferroportin, an iron channel on the surface of enterocytes, hepatocytes, macrophages and placental cells. Another mechanism is direct transcriptional activation of hepatic hepcidin expression via STAT 3 pathway under inflammatory microenvironment [4].

IV. MANAGEMENT OF ANEMIA

Administration of Erythropoietin is initiated when Hb levels fall below 10g/dL and the recommended target Hb to be achieved is between 11 and 12 g/dL. Higher Hb may increase the risk for serious adverse effects including stroke and vascular access thrombosis [5]. In a study Marie Evans et.al suggested that in non-dialysis patients with CKD for Hb <10.0-11.0g/dL ESA initiation is associated with improved survival of patients [6]. Individual patient factors, such as degree of anemia, degree of kidney disease and presence of other adverse factors are some criteria's which makes erythropoietin treatment effective. Mufti Baleegh UR Raheem Mahmood et.al in their study concluded that anemia is highly prevalent in CKD patients and frequent blood transfusion was required despite the use of iron and erythropoietin therapy [7]. rHuEPO is introduced for the treatment of anemia of chronic renal failure(CRF) in 1989. Overall improvement in quality of life (QOL), increased exercise capacity, decreased sleep disturbances and improved cognitive function are some significant impact of rHuEPO [8]. One of the study by Jan Galle suggested that one monthly Continuous Erythropoietin Receptor Activator (CERA) is convenient and effective in non-dialysis and dialysis dependent patients with renal anemia for atleast 2 years. Over the 2-year study period CERA was well tolerated with a good safety profile [9]. Decision about

the preferred route of administration should take into consideration about the severity of anemia and iron deficiency. IV iron administration can lead to a greater increase in Hb concentration, a lower ESA dose or both. Iain. C Macdougall et.al in their study found that a high dose of IV iron regimen administered was superior to a low dose regimen administered and it results in the administration of lower doses of ESA among patients undergoing hemodialysis [10].

Treatment of renal anemia with roxadustat: Even though the administration of erythropoietin stimulating agents and iron supplementation are highly effective therapeutic approach, it has several safety concerns too. Phase 2 and phase 3 trials suggests that roxadustat is well tolerated and clinically effective. Roxadustat can increase endogenous erythropoietin level within physiological range by inducing HIF pathway. By decreasing serum hepcidin and increasing intestinal iron absorption, roxadustat improves iron metabolism [4]. Advantages include roxadustat increases or maintains hemoglobin level effectively regulates iron metabolism, no risk of hypertension, increases endogenous erythropoietin expression in physiological range, avoid side effect induced by iron supplementation.

V. ANEMIA IN CKD – INFLUENCE OF INFLAMMATION

Patients with CKD frequently suffer from chronic inflammatory condition. The underlying factors leading to this condition includes increased level of proinflammatory cytokines, higher incidence of infections, the widespread presence of arteriosclerosis [11]. The persistent inflammation may contribute to the hyporesponsiveness to ESA and thus results in variability in hemoglobin level. Anti-cytokine and anti-oxidative treatment strategies may be used for the treatment of inflammation associated hyporesponsiveness to ESA.

VI. ERYTHROPOIETIN RESISTANCE IN HEMODIALYSIS PATIENTS

The erythropoietin resistant development should be prevented by early detection and elimination risk factors, optimization and individualization of hemodialysis prescription. Resistant to erythropoietin effects is an independent risk factor for the development of acute myocardial infarction, impaired cardiac function and stroke, overall the cardiovascular morbidity [12]. In a study Hideki Kato et.al aims to improve evidence based therapies in non-dialysis CKD patients for renal anemia and this was done by clarifying markers and factors involved in ESA hyporesponsiveness and their relationship with CVD and renal events [13]. Risk factors includes,

6.1 Iron Deficiency: According to the recommendation of KDIGO, IV iron should be administered when the saturation of transferrin with iron-TSAT is less than 30% and serum ferritin concentration is less than 500ng/ml. IV iron administration provide rise in Hb concentration rapidly. When IV iron administered in uncontrolled mannerit can accompanied by accumulation in the liver,

pancreas and heart. Ferric gluconate and iron sucrose are the most two important preparations for the IV use of iron [14].

6.2 Microinflammation: In CKD mild increase in the concentration of proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and Tumor Necrosis Factor alpha (TNF alpha) can be observed [15]. The main cause of developing microinflammation are increased production and decreased clearance of proinflammatory cytokines, metabolic acidosis, oxidative stress, vitamin D deficiency, chronic recurrent infection associated with vascular access, conventional solution for hemodialysis. For achieving and maintaining the target hemoglobin concentration in the blood, certain characteristics should be taken into account and this includes optimization of dialysis treatment, use of dialyzers with polysulphonic membranes and ultra-pure bicarbonate solution for hemodialysis which reduce the serum CRP concentration.

6.3 Vitamin D Deficiency: For the development of erythropoietin resistance, the deficiency of vitamin D is a new risk factor. The normal serum concentration of vitamin D is 3-80ng/ml in patients treated with regular hemodialysis and the serum concentration of less than 30ng/ml indicates the deficiency of vitamin D. Development of secondary hyperparathyroidism, osteoporosis, atherosclerosis, vascular calcification, cognitive function disorder, resistance to erythropoietin effect and anemia, progressive loss of kidney function are the main clinical consequences of vitamin D deficiency in patients with CKD including patients treated with hemodialysis. Cholecalciferol, ergocalciferol can be used to treat vitamin D deficiency in patients receiving hemodialysis. Vitamin D in the serum should be measured once a year for the patients with regular hemodialysis [16].

6.4 Secondary Hyperparathyroidism: The patients who are being treated with hemodialysis, secondary hyperparathyroidism is a common complication. Deficiency of active metabolite of vitamin D, hypocalcemia and hyperphosphatemia are the main factors triggering the development of secondary hyperparathyroidism. Its main clinical consequences are bone disease, cardiovascular disease and the resistance to erythropoietin activity [17,18,19]. For the resistance to erythropoietin activity optimal control of secondary hyperparathyroidism is important. Paricalcitol and cinacalcet reduce resistance to erythropoietin activity and better control of anemia in patients treated with regular hemodialysis.

6.5 Deficiency of Vitamin C: Due to reduced dietary intake and its elimination during hemodialysis, the patients treated with regular hemodialysis have a deficiency of vitamin C [20,21]. Normal serum vitamin C concentration

is 30-60 micromol/l and severe deficiency of vitamin C indicates serum concentration less than 10micromol/l and thus requires replacement of vitamin. IV use of vitamin C reduces the concentration of ferritin and proinflammatory mediators in serum and thus reduces erythropoietin resistance in patients treated with hemodialysis.

VII. CONCLUSION

Anemia is one of the most significant complications of the CKD. Anemia is defined as the level of Hb is reduced than the reference level. Anemia is an important feature of kidney failure because when CKD progresses the function of kidney become worse. Filtration capability of kidney and anemia have direct relationship, lesser the glomerular filtration rate more severe will be anemia. Symptoms include difficulty in breathing, fatigue, poor cognition function, loss of appetite and the immunological response become reduced. It is associated with mortality, CV complications such as LVH and heart failure. The severity and prevalence of anemia increases with decreasing glomerular filtration rate (GFR). Other factors which causes anemia includes iron deficiency, blood loss during dialysis, GI bleeding, deficiency of other hematinics such as vitamin B12 and folic acid. The recombinant human erythropoietin is synthesized by the recombinant DNA technology which resembles both physiologically and structurally to the natural erythropoietin. Iron therapy is indicated to improve the accessible stores for erythropoiesis, to enhance the iron levels in the body and to prevent anemia complications in CRF patients. Anemia is common in hemodialysis patient, develop due to erythropoietin deficiency and leads to morbidity and mortality. Optimal management of anemia improves the quality of life and reduces the hospitalization and death. Anemia management was improved by the introduction of ESA which reduces blood transfusion and iron overload complications. Roxadustat is a novel drug discovered for the management of anemia in CKD.

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