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A REVIEW ON TREATMENT OF RENAL ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND HEMODIALYSIS

Shalini Bahuguna* and Devesh Joshi

India.

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***Corresponding Author**
Shalini Bahuguna
India.

ABSTRACT

Anemia is one of the most common and morbid complications of chronic kidney disease, causing unpleasant symptoms and reducing the quality of life. It is a very common complication of CKD and result in the interference of erythropoietin production. The rate of release of erythropoietin from the kidney is greatly enhanced by various forms of hypoxia, anemia, and carbon monoxide poisoning. Anemia affects 60-80% of patients with renal impairment and is common in both pre-dialysis and on dialysis leading to reduced quality of life and additional risk factor for early death. Treatment with erythropoietin with intravenous therapy in patients receiving haemodialysis, showed that there was a dose dependent rate of response to the hormone. The treatment with recombinant Epo has resulted in a remarkable improvement in global well being and quality of life.

KEYWORDS: Anemia, Hypoxia, Chronic Kidney Disease, Erythropoietin, Hemodialysis, Quality of Life.

INTRODUCTION

Anemia is one of the most common and morbid complications of chronic kidney disease, causing unpleasant symptoms and reducing the quality of life.[1] According to The World Health Organization (WHO), the definition of anemia in general is a hemoglobin value below 130 g/L for males and 120 g/L for non-pregnant women.[2,3] Chronic kidney disease (CKD) is a major public health problem across the world and end-stage renal disease (ESRD) is conventionally considered the most serious outcome of CKD.[4] Prevalence of CKD ranges from 0.79% to 1.4%. Kidneys disease is ranked 3rd amongst life threatening diseases in India, after cancer and heart disease.[5] Different characteristics can be effective to distinguish chronic from acute renal failure. The primary differences between acute and chronic renal

failure are the cause and duration of them.[6] Patients with end-stage renal disease (ESRD) are usually anemic and fail to show an appropriate compensatory erythropoietic response to the anemia.[7,8] Anemia is a very common complication of CKD and is the result of interference of erythropoietin production. However, iron and vitamin deficiencies, blood loss, reduced erythrocyte life span, chronic inflammation, and uremic milieu are also the contributing factors for anemia in CKD patients.[4] Chronic renal failure is also associated with variety of hematological abnormalities. Anemia is the most common, consistent and severe of the various hematological abnormalities. In addition to anemia, patients with chronic renal failure are prone to develop infections and hemorrhagic diathesis. Abnormal haemostasis in chronic renal failure is characterized by tendency to abnormal bleeding and bruising. Decreased factor III activity, abnormal platelet aggregation and adhesiveness and impaired prothrombin consumption contribute to the clotting defect in uremia.[9] The association of anemia with the kidney is important because this organ is responsible both for sensing oxygen availability to tissues and for releasing erythropoietin (Ep) into the circulation. Under normal circumstances, a low level of circulating Ep (10 to 30 milliunits/mi plasma) is capable of maintaining a stable red cell mass.[7] A reduction in haemoglobin concentrations in these patients has been shown to be associated with impairment in quality of life, reduced energy, neurocognitive decline, decreased exercise capacity, and increased mortality. The cause of anaemia in such individuals is mainly related to a deficiency in the synthesis of endogenous erythropoietin.[10] With the advent of recombinant erythropoietin in the late 1980s, it became possible to treat anemia without transfusion, ushering in a new era. It soon became clear that additional considerations were important, such as ensuring adequate iron stores, providing sufficient folate and vitamin B12, and identifying other conditions affecting the hemoglobin level.[11] The kidney releases a hormone, erythropoietin, that stimulates erythrocyte formation in the bone marrow . The rate of release of erythropoietin from the kidney is greatly enhanced by various forms of hypoxia, such as hypoxic hypoxia, anemia, and carbon monoxide poisoning.[12] The anemia of CKD increases morbidity and mortality from cardiovascular complications which may lead to further deterioration of renal function.[13] Red cell production due to the Erythropoietin deficiency is too low in CRF and causes development of anemia in this situation. Anemia is also seen in patients with acute renal failure but the exact relationship between them remained unclear.[6]

Erythropoietin in normal erythropoiesis

In 1957 Jacobson and his colleagues reported that in response to anemia the kidneys produce the then recently described eiythroid growth factor, Epo.[14] Erythropoietin (EPO) is a circulating glycoprotein with a molecular weight of approximately 34,000 daltons which after neonatal life is produced by peritubular endothelial or interstitial cells in the cortex and outer medulla of the kidney.[15] The rate of production of Epo by the kidneys is inversely proportional to the oxygen carrying capacity of blood, and it appears that the unique vascular structure of the kidneys render them extremely sensitive to changes in oxygen supply. This renal sensitivity to oxygen and the capacity of Epo to stimulate the production of oxygen carrying red cells provide an efficient feedback mechanism which maintains an optimal supply of oxygen to the tissues. The gene coding for Epo is located on chromosome 7 and consists of five exons and four introns. Its upstream promoter is apparently not directly responsive to hypoxia but this responsiveness is found in an enhancer located immediately downstream from the gene. Hypoxia initially causes the production of a protein named HIF-1 for hypoxia inducible factor. This factor binds to the oxygen sensitive enhancer and acts as a transcription factor. HIF-1 is produced in response to hypoxia by many different cell types and apparently acts as a general transcription factor for a number of hypoxia inducible genes, such as those coding for platelet derived growth factor and vascular endothelial growth factor as well as for many glycolytic enzymes. Epo indistinguishable from that produced by the kidneys can also be produced by hepatocytes and macrophages and possibly even by erythroblasts. Although the rate of production of Epo is clearly related to the degree of anemia and in turn to the supply of oxygen to the tissues, this relationship is quite broad, suggesting that a number of other factors play a role. It would seem likely that toxic metabolites retained in patients with chronic renal disease may also impair activation of the Epo gene hut relevant observations are not available.[14]

Assessing kidney function and renal risk factors

Three aspects of renal function are pivotal to assess kidney dysfunction: (1) an estimate of the filtration of the kidney; (2) quantification of proteinuria; and (3) urinalysis. The glomerular function rate (GFR) can be assessed in a number of ways, which are all based on the unique properties of creatinine. One way is to estimate the creatinine clearance by a 24-hour urine collection, and plasma and urine determinations of creatinine. There are inherent limitations with this estimation are urine collection errors and, at very low clearances, overestimation of GFR by creatinine secreted into the tubules. Frequently used is the Modified Diet of Renal

Disease (MDRD) formula to calculate the GFR of a patient; it uses the age, sex, ethnicity and an equation based on epidemiological data. This method is currently being further refined and developed, since it was derived from CKD patients and has a limited accuracy in people with a GFR >60 mL/min/1.73m2. The gold standard for the measurement of GFR is the inulin infusion technique. Inulin lacks one of the limitations of creatinine, as it is solely filtered.[16]

Iron deficiency in patients with renal failure

The anemia of renal failure is caused by the lack of sufficient quantities of endogenous erythropoietin. With the availability of recombinant human erythropoietin (rHuEPO) however, it has become apparent that to achieve a given target, hematocrit requires proper management of iron replacement, as well as the administration of rHuEPO. Iron deficiency, either absolute or functional will occur in most, if not all, patients on hemodialysis receiving rHuEPO because of the increased demand for iron in a group of hemodialysis patients receiving rHuEPO driven by the accelerated erythropoiesis that occurs with exogenous rHuEPO administration, coupled with ongoing blood losses from dialyzer and tubing, blood sampling, gastrointestinal blood loss, and blood losses at the time of dialysis needle placement and removal.[17]

Recombinant Human Erythropoietin (rHuEPO)

Structural and biological characteristics

Erythropoietin in blood is mainly of renal origin, with a small amount derived from the liver. The human erythropoietin gene is situated at chromosome 7q11-22, consisting of five exons and four introns, which produces a post-transcriptional single polypeptide containing 193 amino acids. During the post-translational modification, glycosylation occurs with the addition of three N-linked (atAsn-24,Asn-38andAsn-83) and one O-linked (at Ser-126) acidic oligosaccharides, the formation of two disulphide bonds at Cys-7 to Cys-161 and at Cys-29 to Cys-33, concomitant with the removal of the 27 amino acid hydrophobic secretory sequence. The Arg-166 at the COOH terminal is believed to be cleaved before the release of erythropoietin into the circulation, with the primary structure of a mature erythropoietin (andhence rHuEPO) containing165 aminoacids.(fig 1).

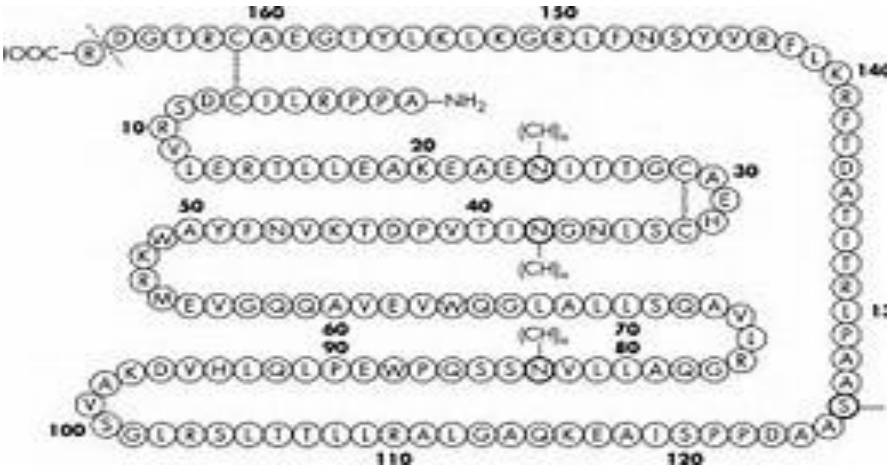

Figure 1; Primary structure of erythropoietin (RHuEPO). (CH)n, N-linked glycosylation site at aspartyl residues 24, 38, 83; (CH)o, O-linked glycosylation site at seryl residue 126. NB: The ARG-166 at the carboxyl terminal is removed before erythropoietin is released into the circulation.

The molecular mass of the polypeptide backbone and the glycosylated form of erythropoietin is estimated to be 18 kDa and 30 kDa respectively. Circular dichroism spectral analysis has proposed that its secondary structure contains 50% of α-helix moiety, with spatial arrangement of two α-helical pairs running antiparallel similar to that of growth hormone. The glycosylated (or sugar) moiety of erythropoietin has an important role in terms of biosynthesis, tertiary structure of the molecule, and in vivo biological activity.[18]

Clinical applications of RHuEPO

• Replacement therapy (low endogenous erythropoietin level) in anaemia associated with.

(A) Chronic renal failure (B) Malignancy (C) Prematurity (D) HIV infection.

• Supportive therapy (to maintain/accelerate erythropoiesis) in.

(A) Post-chemotherapy/post-radiotherapy (B) Post-transplantation

• Augmentative therapy (increase haemoglobin above physiological level) in.

(A) Surgery (B) Situations where blood transfusion is refused/disallowed

(C) Sport (potential abuse by athletes)

• To enhance autologous transfusion so as to maintain haemoglobin perioperatively.

• Other potential therapeutic applications.

(A) Anaemia associated with-autoimmune diseases, acute haemolysis, haemoglobinopathy. (B) Acute renal failure. (C) Critically ill patients. (D) Neuroprotection. (E) Congestive cardiac failure.[18]

Epidemiology

Prevalence of CKD ranges from 0.79% to 1.4%. Anemia affects 60-80% of patients with renal impairment and common in both pre-dialysis and on dialysis leading to decreased exercise tolerance, reduced quality of life and additional risk factor for early death.[5] Although the prevalence of anemia increases with diminishing renal function, a normochromic and normocytic anemia already can be observed at a relatively early stage of renal dysfunction. Both the Third National Health and Nutrition Examination Survey 111 and the National Kidney Foundation: Kidney Early Evaluation Program showed that therisk of anemia significantly increases when the Glomerular Filteration Rate decreases to less than 60ml/min.[19] Anemia is a common finding in patients with CKD, with a prevalence that increases gradually as GFR declines. Data on the prevalence of renal anemia differ significantly, depending in large part on the size of the study, the selection of participants (general population versus patients already under a physician's care, the definition of anemia and whether they do or do not have diabetes).The National Health and Nutrition and Examination Survey (NHANES) III database was used in 2 different studies that examined the relationship between prevalent Hb concentration and GFR; their results are consistent with those obtained in ambulatory adult patients. Diabetic status affects the prevalence of anemia in patients with CKD.[20]

Aetiology-Pathogenesis

Anemia in CKD is due primarily to reduced production of erythropoietin in the kidney (a reflection of reduced renal mass) and secondarily to shortened red cell survival. In humans, EPO is produced by peritubular cells in the kidneys of the adult and in hepatocytes in the fetus. These cells (located at the tip of the renal pyramids, susceptible to ischemia), are sensitive to hypoxia that once sensed leads to an increase in EPO production. Although several tissues are able to produce EPO, the main source of EPO is the kidney due to its ability to regulate the hematocrit by matching the plasma volume and the red blood cell (RBC) mass. EPO circulates in the plasma and induces red cell production in the bone marrow8, where it binds to erythroid progenitor cells.[20] The most critical change that occurs with hemodialysis is reduction of extracellular volume by ultrafiltration. Failure to control extracellular volume adequately is the major long-term contributor to morbidity and mortality in patients with end-stage renal disease.[21]

Evaluation of the patient with renal anemia

Since erythropoietin is not the only cause of anemia in CKD patients, the initial evaluation should include a variety of tests that provide information about the activity of the bone marrow, the adequacy of iron stores and the vailability of iron for erythropoiesis.

• Haemoglobin
• Mean corpuscular haemoglobin (MCH)
• Mean corpuscular volume (MCV)
• Mean corpuscular haemoglobin concentration (MCHC)
• White blood cell count (WBC) and differential
• Platelet count
• Absolute reticulocyte count
• Serum ferritin
• Serum transferring saturation (TSAT) or content of Hb in reticulocytes (CHr)
• B12 and folate blood levels The initial evaluation of the patients with anemia and CKD should include the analysis of the complete blood count (CBC) that gives valuable information about the severity of anemia, the adequacy of nutrients and the function of bone marrow.[20,22,23]

Erythropoietin deficiency and inhibition of erythropoiesis in renal insufficiency

The relative importance of erythropoietin (Ep) and inhibition of erythropoiesis in the anemia of chronic renal insufficiency has been investigated. Sixty patients with varying degrees of renal insufficiency, 40 normal subjects and 40 patients with anemia and normal renal function, were studied. Studies of granulopoiesis showed uremic sera supported in vitro CFUGM growth more efficiently than sera from normal subjects. These results suggest that inhibition of erythroid, but not granulocytic, progenitor cell formation, in addition to a relative erythropoietin deficiency, are the primary factors responsible for the anemia of chronic renal failure. Although the anemia of chronic renal failure is a complex disorder in which many factors may play a role , the main defect is absolute or relative EPO deficiency. In most patients with impaired renal function, EPO production is impaired at any given hematocrit concentration.[19,24]

Pathophysiology: Traditional thinking has ascribed the anemia of chronic renal failure to four mechanisms.

(1) Epo deficiency (2) shortened red cell survival (3) retained inhibitors or toxic metabolites that inhibit erythropoiesis and (4) blood loss resulting from the qualitative platelet defect present in uremia.[19,25]

Epo deficiency: It is unquestionably a major mechanism of this anemia. Ninety percent of Epo normally is made in the kidney, and only 10% is produced in the liver. When renal disease develops, maximum Epo secretion presumably is blunted, even when Epo production is stimulated by hypoxia caused by anemia or other forms of impaired oxygen delivery.[26] Renal disease usually disrupts this orderly sequence and results in a submaximal Epo response to an anemic stimulus.

Bone marrow inhibition: Inhibitors of erythropoiesis play a significant causal role in this anemia. If present, such inhibitors could blunt or even block the effect of Epo. Four lines of evidence suggest the presence of erythropoietic inhibitors in patients with chronic renal disease. (1) In-vitro erythropoiesis is impaired when uremic serum is incubated with murine marrow cells in the presence of growth factors, including Epo (2) levels of bioactive Epo in the plasma of some anemic hemodialysis patients are elevated (3) infusion of Epo-rich plasma from a patient with aplastic anemia into several patients with advanced renal failure and anemia failed to elicit a reticulocytosis and (4) a higher proportion of patients treated with continuous ambulatory peritoneal dialysis (CAPD) achieve normal hematocrit levels than do hemodialysis patients.[25,27]

Shortened red-cell survival: Red-cell hemolysis, although mild, can contribute to the anemia. Redcell half-life, however, as quantified by 51chromium labeling, occasionally is normal. Most radioisotopic studies (using chromium DF32P, or '4C cyanate) confirm the presence of mild hemolysis. The cause of the hemolysis is not known. Studies 30 years ago suggested that some intravascular substance(s) retained in patients with advanced renal failure shortened red-cell survival; when red cells from a patient with advanced renal failure are infused into a normal subject, redcell life span is restored to normal. Neither hemodialysis nor peritoneal dialysis significantly improves red-cell survival. In the presence of normal kidneys, increased Epo secretion would easily compensate for such a mild degree of hemolysis.[25,28]

Bleeding: Significant blood loss occurs in as many as 25% of patients with progressive renal failure and can contribute to their anemia. The major reason for this increased bleeding is the

qualitative platelet defect that develops in azotemic patients accounting for blood loss from the gastrointestinal tract, within the skin, and from other sites.[29] Platelet dysfunction prolongs the bleeding time and impairs platelet aggregation in vitro. Several mechanisms can be invoked to explain this platelet dysfunction: decreased platelet factor 3 activity, decreased platelet levels of thromboxane A2, an increase in prostacyclin (PGI2) (an inhibitor of platelet aggregation derived from the vascular endothelium) and suboptimal Factor VIII:von Willebrand complex activity.[30]

Starting dose of erythropoietin and route of administration: Most experience of treatment with erythropoietin is with intravenous therapy in patients receiving haemodialysis, and one of the earliest studies showed that there was a dose dependent rate of response to the hormone. It has become increasingly apparent, however, that the risk of side effects such as severe hypertension and thrombotic complications is lessened when the rise in haemoglobin concentration is about 10 g/l/month. Erythropoietin is usually prescribed in doses of 100-200 U/kg/week for patients receiving haemodialysis, divided into two or three intravenous doses. A similar intravenous dosage regimen has been used with good effect in patients not yet receiving dialysis. The intravenous route is clearly impractical for chronic use in patients having continuous ambulatory peritoneal dialysis who have no ready vascular access. The intraperitoneal and subcutaneous routes are obvious alternatives. In patients receiving continuous ambulatory peritoneal dialysis the bioavailability of erythropoietin given subcutaneously in a single dose was found to be seven times greater than when it was given intraperitoneally but was still only 22%.

The subcutaneous route seems to be efficacious not only in patients receiving continuous ambulatory peritoneal dialysis but also in those receiving haemodialysis, and the evidence to this suggests that lower doses of erythropoietin may be used when given by this route. Further studies are required, but on the evidence available a starting dose in the range of 25-75 U/kg given subcutaneously twice or thrice weekly seems suitable. If patients can be taught to give their own injections, then a daily dosing regimen 33 may be worth considering.[31,32]

Treatment with erythropoietin: The management of renal anemia has been revolutionized over the last 15 years, after the recombinant human erythropoietin (rHuEpo) was introduced which replaced blood transfusion as the mainstay treatment of this complication. Specific clinical guidelines have been developed to optimize the quality of anemia management secondary to CKD.[30] To date, there has been no satisfactory treatment for the anemia of

ESRD. Red cell transfusions have been the only sure way to correct the symptoms of tissue hypoxia, but such therapy is only transiently effective and transfusions increase the risk of exposure to hepatitis or other infectious agents.[33] In the past, a few attempts were made to treat patients with Epo isolated from the urine of anemic individuals however, it was in the middle 80's with the availability of recombinant human Epo that clinical trials became possible. Since then replacement therapy with recombinant human Epo has become the most rational therapy for the anemia of chronic renal failure worldwide. The treatment with recombinant Epo has resulted in a remarkable improvement in global well being and quality of life. Erythroid marrow suppression may be another effect of transfusion therapy, especially if multiple units of red cells are infused at once.[34] Furthermore, the elimination of anemia has been beneficial for a number of co-morbid conditions introduced by the aging and prevalence of diabetes among patients initiating dialysis. This global success in dialysis patients has motivated the subsequent use of recombinant human Epo in pre-dialysis patients showing progressive renal failure. The core treatment of renal anemia is to fuel erythropoiesis by regular injections with erythropoiesis stimulating agents (ESAs) and to secure sufficient iron availability for proper erythropoiesis.[35] Numerous studies have indicated that ESA therapy results in an improvement in the patient's quality of life. As a result, ESA treatment is a routine management component for hemodialysis patients, and is frequently used in nondialysis CKD as well.[36] Initial concerns of accelerating renal function deterioration in patients with progressive renal failure have not been substantiated. No significant alteration in the progression of renal disease has been noted. However, avoidance of renal function deterioration requires careful control of blood pressure before or soon after starting recombinant human Epo through the aggressive use of antihypertensive agents. Slow correction of anemia by using lower starting doses is advocated by some since such an approach, particularly in children, tends to improve the glomerular filtration rate as assessed indirectly. The mechanisms producing hypertension with recombinant human Epo therapy are likely to be multifactorial: loss of hypoxic vasodilation, changes in blood viscosity, in activation of renin-angiotensin system, in blood volume, or through a direct vascular effect. This last mechanism may involve increased synthesis of endothelin-1, increased vascular calcium uptake, and platelet-dependent mitogenic action. The role of recombinant human Epo therapy in raising plasma endothelin-1 to levels, which directly can increase pressure remains controversial. Nevertheless, if body wt and interdialytic fluid gains are controlled in dialysis patients, systolic and diastolic blood pressure remain virtually unchanged despite significant increases in hematocrit. Similar observations have been reported for predialysis

patients. Many of these predialysis patients need aggressive diuretic therapy during recombinant human Epo treatment to maintain constant blood volume and thus avoid hypertension. Regular hemodialysis therapy (RDT) and continuous ambulatory peritoneal dialysis (CAPD) have both been reported to lead to an improvement in the anemia associated with endstage renal disease.[37,38] Regression of left ventricular hypertrophy (LVH), reduction of left ventricular volume and improvement in exercise induced ST-segment depression may occur following partial correction of anemia.[38]

CONCLUSION

After reviewing several articles it was seen that anemia is one of the most common and morbid complications of chronic kidney disease, causing unpleasant symptoms and reducing the quality of life of patients. In this review, we have conveyed concerns about treatment of Renal Anemia in Patients with chronic Kidney Disease and Patients undergoing Hemodialysis and what anemia management should be about: optimizing clinical outcomes, including quality of life, and minimizing risks, while maintaining public trust by achieving our clinical goals in the most cost-effective way possible. Appropriate management of anemia will not only have a positive impact on quality of life but also reduce hospitalizations of CKD patients due to cardiovascular events.

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