

Erythropoietin's Influence on Renal Anemia Treatment: Review Article

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ABSTRACT

Background: The main chain of erythropoietin (EPO) consists of 193 amino acids and it has a molecular weight of 34000 Dalton (Da). EPO is a hormone-like molecule that is secreted primarily by renal interstitial cells, with the liver contributing the remaining 10%. Renal tubular or glomerular injury can restrict EPO production and create renal tissue hypoxia, which can then lead to an increase in the production of EPO in the serum. EPO is a humeral factor that enhances red blood cell production by increasing bone marrow cell proliferation and differentiation. Blood flow into peripheral blood arteries can also be boosted by EPO's ability to differentiate stem cells into red blood cells. After being activated by its receptors, to create adult hemoglobin, erythroid cells need to be differentiated and proliferated. EPO aids in the differentiation and proliferation of these cells.

Objective: To determine if erythropoietin could be useful in the treatment of renal anemia.

Methods: The databases were searched for articles published in English in 3 data bases [PubMed – Google scholar-Egyptian knowledge bank] and Boolean operators (and, or, not) had been used such as [Erythropoietin and Renal Anemia OR EPO] and in peer-reviewed articles between July 2002 and May 2021.

Conclusion: Renal anemia patients who receive EPO treatment can have considerable improvements in oxygen levels, immunological function, and so on; An iron overload or blood infection can be prevented by using EPO in transfusions.

Keywords: Erythropoietin, Renal Anemia.

INTRODUCTION

It's common for youngsters with renal illness to suffer from anemia. When the glomerular filtration rate drops below 60 mL/min per 1.73 m², hemoglobin levels drop as well, and this is particularly prominent in adults. The association between GFR and anemia is less evident in children. For both adults and children, erythropoietin and iron therapy has made it possible to forego routine blood transfusions in order to maintain a patient's hemoglobin level. Numerous research in adults and comparatively few in children have shown that higher hemoglobin levels are linked to greater quality of life, cognitive function, exercise ability, and cardiovascular health ⁽¹⁾.

More than 170 years ago, Richard Bright first connected anemia to chronic kidney disease (CKD). Nearly all patients with CKD stage 5 develop anemia as their kidney disease progresses. Having anemia as a result of chronic renal disease increases one's risk of cardiovascular illness, in-patient stays in the hospital, mental decline, and even death ⁽²⁾.

A normocytic, normochromic, and hypoproliferative anemia is common in people with kidney disease. A lack of erythropoietin in individuals with chronic kidney disease (CKD) has been attributed to the discovery in the 1950s of a circulating factor that stimulates erythropoiesis and the kidney as the primary source of erythropoietin. Development of immunologic assays for quantifying circulating EPO levels in the late 1970s and early 1980s was made possible by EPO purification and cloning. EPO levels are considered abnormally low in anemia of CKD, despite the fact that anemic individuals with normal kidney function had EPO levels 10–100 times higher than those with CKD. Assays like this one measure all immunogenic EPO fragments, which don't all correlate with biological activity ⁽³⁾.

Erythropoietin's main chain has a molecular weight of 34000 Da and is composed of 193 amino acids. Renal interstitial cells are the primary source of EPO, with the liver accounting for the remaining 10%. Damage to the renal tubules or glomeruli can result in renal tissue ischemia and hypoxia, which can prevent the generation of EPO and increase the amount of EPO produced in the bloodstream. EPO enters the body's metabolic pathway as soon as it is created. An abnormality in the hemoglobin and hemoglobin pressure feedback regulation, prolonged rise in serum EPO levels leads to kidney damage in the human body ⁽⁴⁾.

EPO can increase bone marrow cell proliferation and differentiation, and it is a humeral factor that promotes red blood cell production. Red blood cell development and blood flow into peripheral blood arteries can also be facilitated by EPO, which is a growth factor for stem cells. EPO can increase bone marrow cell proliferation and differentiation, and it is a humeral factor that promotes red blood cell production. Red blood cell development and blood flow into peripheral blood arteries can also be facilitated by EPO, which is a growth factor for stem cells ⁽⁵⁾.

Effects of Erythropoietin and Other Substances Taken Together:

Iron sucrose:

The clinic offers two main therapy options: oral iron supplements and intravenous iron supplements. Individuals with uremia and digestive tract iron release and iron malabsorption issues generally fail to achieve EPO therapy needs when delivered orally using the reticuloendothelial system. Intravenous iron supplementation can bypass the reticuloendothelial

system iron release barrier, which has high utilisation rates and low gastrointestinal reactivity ⁽⁶⁾.

Intravenous iron complexes are helped to release iron ions by activated macrophages in the reticuloendothelial system. Immature red blood cells have transferrin and transferrin receptors on their surface, which binds the other component of iron to form serum ferritin, which accelerates iron utilisation in these processes and increases the body's iron reserves in these processes. Sucrose iron treatment has an unpleasant reaction after low and minor occurrences, but clinical observation has shown that treating first with EPO and subsequently increasing therapy with sucrose iron can improve clinical efficacy significantly ⁽⁷⁾.

L-carnitine:

As an amino acid that's already in your system, L-carnitine has been shown to boost the body's response to various conditions by altering membrane phospholipid and erythrocyte deformation capacity, stabilising red-cell membrane and increasing hematocrit levels. Lack of L-carnitine in cells produces toxic effects, increases the osmotic fragility of normal red blood cells, decreases life expectancy, and may lead to EPO resistance. Following nine months of treatment, significant increases in hemoglobin (Hb) have been observed in patients receiving long-term intravenous L-carnitine supplementation together with long-term usage of EPO in hemodialysis. L-carnitine improves membrane stability, reduces brittleness, and prolongs the life of red blood cells by decreasing erythrocyte lipid composition, which is most likely why it has such an effect⁽⁸⁾. In both erythrocyte fat conversion and oxidative phosphorylation, supplementation with L-carnitine can be beneficial. L-carnitine's actions on red blood cell progenitor cells in the bone marrow may also enhance EPO's therapeutic power. This treatment has been demonstrated to ameliorate renal anemia by lowering CRP, IL-1, and TNF levels in cancer patients in remission as well as reducing microinflammation⁽⁹⁾.

Iron dextran:

A form of intravenous iron therapy known as iron dextran. Erythropoietin treatment results in an increase in iron utilisation and an imbalance in iron storage in the body in anemic patients. Acute and long-term adverse reactions to intravenous iron supplementation, such as breathing difficulties, hypotension, heart palpitations, vasogenic edoema, and urticaria, might occur. L-carnitine injection with erythropoietin, along with iron dextran dispersion tablets, can dramatically boost EPO efficacy, improving anemia and lowering dialysis syndrome by reducing the amount of EPO in the blood ⁽¹⁰⁾.

Reduced glutathione:

Low glutathione levels and high oxidised glutathione concentrations are all associated with lower antioxidant activity and increased oxidative glutathione

in patients with chronic renal failure. Disulfide linkages between red blood cell membrane molecules cause macromolecules to cluster, resulting in red blood cell deformation ⁽¹¹⁾.

Cysteine, glutamic acid, and glycine make up the tripeptide glutathione, which plays a crucial role in metabolic control in cells. Thiol and cysteine can be supplied, normal metabolism and physiological functions can be maintained, and the integrity of the cell membrane can be preserved. Lipid peroxide can also be eliminated by combining with pro electrons or reactive oxygen species. Chronic renal failure can be treated with exogenous reductive glutathione, which reduces oxidised glutathione levels, lowers the oxidized/reduced glutathione ratio, stabilises the red blood cell membrane, and extends the life of red blood cells. Erythropoietin alone has been proven to have a smaller effect on anemia than reductive glutathione ⁽¹²⁾.

Vitamin C:

There, water-soluble vitamin C, or ascorbic acid, is absorbed in the upper region of the small intestine by the body. The significance of vitamin C in oxidative reduction benefits metabolic responses substantially. Vitamin C, present in citrus fruits, affects a number of processes, including collagen synthesis, scurvy prevention, gum and mouth health maintenance and prevention, arterial hardness prevention, antioxidant production and anemia therapy. Vitamin C lowers ferric iron levels, making it easier for the body to absorb it in the intestines and liver. Some hemodialysis patients' dialysis clearance is lowered when they are deficient in vitamin C ⁽¹³⁾.

Intravenous vitamin C helps reduce iron overload in anemic patients by increasing hemoglobin levels. When using vitamin C, some people have had side effects such as an increase in serum uric acid, urinary tract stones, and reduced fertility ⁽¹⁴⁾.

Trace element copper:

Copper is a vital component of the human body, with an average of 70 to 100 mg each person. Iron intake, usage, and storage are all strongly linked to copper in the body during hematopoiesis. Copper may turn ferric iron into organic iron, allowing it to be pushed into the bone marrow where it speeds up the creation of hemoglobin and porphyrin from storage. Immature cells can be accelerated in their maturation and released faster if copper is added to the mix. Patients with low EPO response who have renal failure and anemia should be given copper supplements to enhance iron utilisation, however this has only been proven in animal studies and has to be tested in clinical trials ⁽¹⁵⁾.

Erythropoietin stimulating agents (ESA):

As a result of the usage of ESAs, the number of individuals with transfusion-dependent anemia has been virtually eliminated. Even though ESA therapy has made significant progress, its therapeutic application can be

termed non-physiological in terms of dosage, time, and manner of administration. As a result, if a target increase in hemoglobin concentration was not obtained after 2 to 4 weeks of treatment with ESA, the dosage was increased. Instead of boosting endogenous EPO levels, which is the body's normal reaction to anemia, this treatment increased the risk of harmful side effects⁽¹⁰⁾.

Mechanism of action:

Endogenous and exogenous erythropoietin and erythropoietin-stimulating drugs enhance erythroid progenitor cell division and differentiation. CD34+ hematopoietic stem cells, which are extremely early erythrocytes, have EPO receptors on their surface. To activate genes that promote cell proliferation and prevent cell death, natural EPO or its recombinant analogues attach to the receptor on the cell surface. The end outcome is a rise in total hemoglobin and hematocrit levels in the bloodstream⁽¹⁶⁾.

Hemoglobin (Hb) target:

Three major clinical investigations emphasise the hazards associated with ESA medication. The US Normal Hematocrit experiment was the first prospective, randomized study to see if ESA medication may help normalise hemoglobin levels in the blood⁽¹⁷⁾.

Randomized into two groups, 30 percent and 42 percent of patients on chronic dialysis were assigned to each group and observed until the development of either death or first nonfatal myocardial infarction, the primary endpoint of this study. Trial was terminated early due to a higher number of patients in the higher goal group reaching the primary endpoint, thereby negating any advantage in "normalising" the hematocrit and revealing that therapy with ESA may in fact be harmful to patients. Other clinical outcomes, such as an increase in vascular access thrombosis, imply that the traditional hematocrit therapy paradigm has additional detrimental implications⁽¹⁸⁾.

Next, a major randomised controlled clinical trial was conducted to see if changing hemoglobin treatment objectives (11.3 g/dl vs. 13.5 g/dl) altered clinical outcomes in 1432 patients with CKD stages 3 and 4 who were randomly assigned to one of two hemoglobin therapy groups⁽¹⁹⁾. High-target hemoglobin patients were more likely to experience congestive heart failure, hospitalisation, stroke or myocardial infarction than low-target hemoglobin patients; however, there was no difference in quality-of-life scores between the two groups.

Most recent large trial investigating the risks and benefits of ESA medication, the 2009 Trial to Reduce Cardiovascular Events with Aranesp Medication, included 4038 patients with type 2 diabetes and CKD stage 3 or 4 who were randomly assigned to receive either darbepoetin or a placebo injection. The goal hemoglobin level was 13.0 g/dl. After a median of 29.1 months of follow-up, The primary outcome (death, nonfatal myocardial infarction or stroke, heart failure, or

unstable angina) was not reduced in the darbepoetin-treated arm, and there were considerably more strokes, death from recurrence of cancer, and venous and arterial thromboembolic events in comparison to the placebo group⁽²⁰⁾, all that darbepoetin therapy provided was less transfusions and an improvement in fatigue.

Despite the known or suspected risks of using ESAs, it was hypothesised in each of these investigations that increasing hematocrit or hemoglobin by administering ESAs would have considerable clinical advantages. Although higher hemoglobin targets correspond to higher total ESA doses, analyses of major trial data have revealed that the high ESA doses delivered may be a primary mediator of harm, rather than the specific hemoglobin target⁽²¹⁾.

Recombinant human erythropoietin (rHuEPO): Structure and Mechanism of Action:

Human erythropoietin recombinant (rHuEPO) is a glycosylated protein of 165 amino acids and a molecular weight of 30,400 Dalton. The molecule's bulk is made up of 60% amino acids and 40% carbohydrates. The molecule's carbohydrate is located on oligosaccharide chains with one or three oligosaccharide links. Sialic acid, a negatively charged sugar molecule, is commonly found at the end of these chains. Sugar molecules in general have no sialic acid residues, hence this is an important factor in determining how negatively charged the molecule is overall. For structural reasons, rHuEPO can include no more than 14 sialic acids⁽²²⁾.

Darbeoietin alpha:

Structure and mechanism of action:

Hyperglycosylated erythropoietin analogue darbepoetin alfa is used to treat anemia in individuals with chronic renal failure or those receiving cancer treatment, and it has the same indication as EPO. In order to increase the half-life of darbepoetin alfa by threefold (t12), two extra N-glycosylation sites (Asn30 and Asn88) were introduced into EPO using site-directed mutagenesis in five amino acids (Ala30Asn, His32Thr, Pro87Val, Trp88Asn and Pro90Thr). Consequently, darbepoetin alfa is administered less frequently than EPO in treatment, which enhances patient convenience⁽²³⁾.

Darbepoietin alpha in pediatrics:

Darbepoetin alfa has essentially replaced rHuEpo in older children and people with CKD in the past decade. But there are few reports on the safety and effectiveness of darbepoetin alfa in infants under the age of one year with CKD⁽²⁴⁾.

Complications of ESA:

In the early days of dialysis, the use of ESAs has been linked to hypertension, seizures, and vascular access thrombosis. Following this, the use of ESAs was connected to "overshooting" of hemoglobin, resistance to ESAs, hemoglobin cycling, strokes, and cancer

connections. A number of mechanisms for ESA toxicity have been hypothesised, but the difficulty in detecting high blood pressure caused by ESAs and the high underlying risk of death from cardiovascular events and probably even neoplasia in dialysis patients have obscured these findings to some extent ⁽²¹⁾.

CONCLUSION

Renal anemia patients who receive EPO treatment can have considerable improvements in oxygen levels, immunological function, and so on; the use of EPO can prevent transfusion-related problems, such as iron overload or blood infection.

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