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EPO Administration to CKD Patients with Anemia

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Abstract: ***Chronic Kidney Disease (CKD) is leading public health problem worldwide. Even though CKD can be prevented or delayed by taking preventive measures, early detection and treatment; the most common problem which occurs in CKD patients is anemia that increases morbidity & mortality. Anemia mostly occurs due to decreased erythropoietin production which can be corrected by administration of recombinant human erythropoietin, commonly known as Erythropoietin Stimulating Agents (ESA), like epoetin alfa, however oxidative stress and inflammation causes treatment resistant anemia & other adverse outcomes. Other factors like inadequate hemodialysis high dose of epoetin, failing to control HB levels are associated with suboptimal response to erythropoietin therapy In this review, we have outlined variety of issues need to be taken into consideration when prescribing ESA for treating anemia in CKD patients.***

Keywords: Chronic Kidney Disease, Anemia, Erythropoietin Stimulating Agents, Oxidative Stress, Haemodialysis

1. Introduction

Recombinant human erythropoietin (rHuEpo) was introduced in 1989 to treat the anaemia associated with chronic renal failure **(1)** Erythropoietin, a glycosylated protein hormone produced primarily by the order, is the primary regulator of red blood cell (RBC) production (erythropoiesis). It promotes the production of red blood cells by increasing the survival, proliferation, and isolation of erythroid progenitors in hematopoietic tissues (bone marrow). **(2)** Recombinant mortal EPO (rHuEPO) was developed in the 1980s and quickly became the leading medicine for treating anaemia associated with CKD, nearly eliminating the need for RBC transfusion. **(3)** Later on, it was also used to treat anaemia associated with critical illness. **(4)** HIV infection, as well as major surgical procedures **(5),** as well as chemotherapy - treated cancer cases. **(6)** Ongoingpre - clinical and clinical trials are exploring the implicit use of rHuEPO as a tissue defensive agent in the brain, heart, kidney, and in wound healing. (**7, 8, 9, 10)** rHuEPO has been used in sports to improve performance and compliance. Increased RBC abundance as a result of rHuEPO use results in increased oxygen delivery and muscle activity. rHuEPO has been used in sports to improve performance and compliance. Increased RBC abundance as a result of rHuEPO use results in increased oxygen delivery and muscle activity. **(11)** The use of rHuEPO in sports has been prohibited by the International Olympic Committee since 1990; however, Lasne and de Ceaurriz developed a direct discovery system that could effectively separate endogenous and recombinant EPO in the decade that followed. (**12)** The detection system is based on IEF - PAGE and double immunoblotting with the highly sensitive anti - EPO monoclonal antibody AE7A5. **(13)** It was first used in the Sydney Summer Olympic Games in the year 2000. **(14)** Other methods, in addition to IEF - PAGE, are used for EPO characterization of biosimilars and copy epoetins. Among them is ELISA, (**15)** MAIIA, SDS - PAGE, and Sarcosyl - PAGE (Membrane Assisted Iso - form ImmunoAssay). **(16)**

An examination of the relationship between anaemia and negative outcomes:

As previously stated, it has been widely assumed that anaemia in CKD populations contributes to unfavourable outcomes due to the positive relationship between anaemia severity and those outcomes. It is important to highlight that EPO and iron preparations are typically used to treat anaemia in dialysis - dependent CKD patients. Therefore, rather than being caused by a lack of medication, EPO resistance is a common cause of severe persistent anaemia in this population. . Inflammation, a prevalent trait of severe renal insufficiency, is a common cause of CKD patients' poorly responding anaemia. **(17, 18)** They are capable of causing anaemia, cardiovascular disease, as well as other illnesses all at once (Figure 1). Comorbid conditions include Diabetes, hypertension, autoimmune diseases, and systemic and local infections (such as hepatitis, infected hemodialysis blood access, and infected peritoneal catheters) commonly worsen the oxidative stress and inflammation caused by chronic renal failure (CRF). By promoting endothelial dysfunction, hypertension, atherosclerosis, and a variety of other diseases, oxidative stress and inflammation increase the risk of morbidity and mortality from cardiovascular diseases and other causes. For example, oxidative stress and inflammation promote lipid and lipoprotein oxidation, endothelial cell activation, adhesion, infiltration, and transformation, all of which contribute to the development of atherosclerosis of

monocyte to foam cells, vascular smooth muscle cell migration, proliferation, and phenotypic change, formation of plaque and rupture or release of matrix metalloproteinases and ultimately thrombosis [**19, 20]**. Furthermore, inflammation and oxidative stress reduce HDL - mediated reverse cholesterol transfer, as well as HDL's anti - inflammatory and anti - oxidant properties. [**21]**. The following mechanisms explain how oxidative stress and inflammation together lead to EPO - resistant anaemia [**22, 23, 24]**: (i) Shorter erythrocyte life span due to breakdown of erythrocyte phospholipids in the membrane and redox capability, (ii) Hepatic hepcidin production, which, when bound to ferroportin, prevents intestinal iron absorption and mobilisation. **[22]**, (iii) Reduced transferrin production, resulting in decreased iron availability, and (iv) Resistance to EPO's Erythropoietic Activity.

Therefore, a substantial connection between anaemia and cardiovascular disease in the presence of inflammation mostly indicates their surrogacy rather than a causal relationship. However, it should be emphasised that severe anaemia might worsen the signs Increased cardiac output. This results in left ventricular dilatation and heart failure. and, by increasing cardiac output, cause left ventricular dilatation and heart failure.

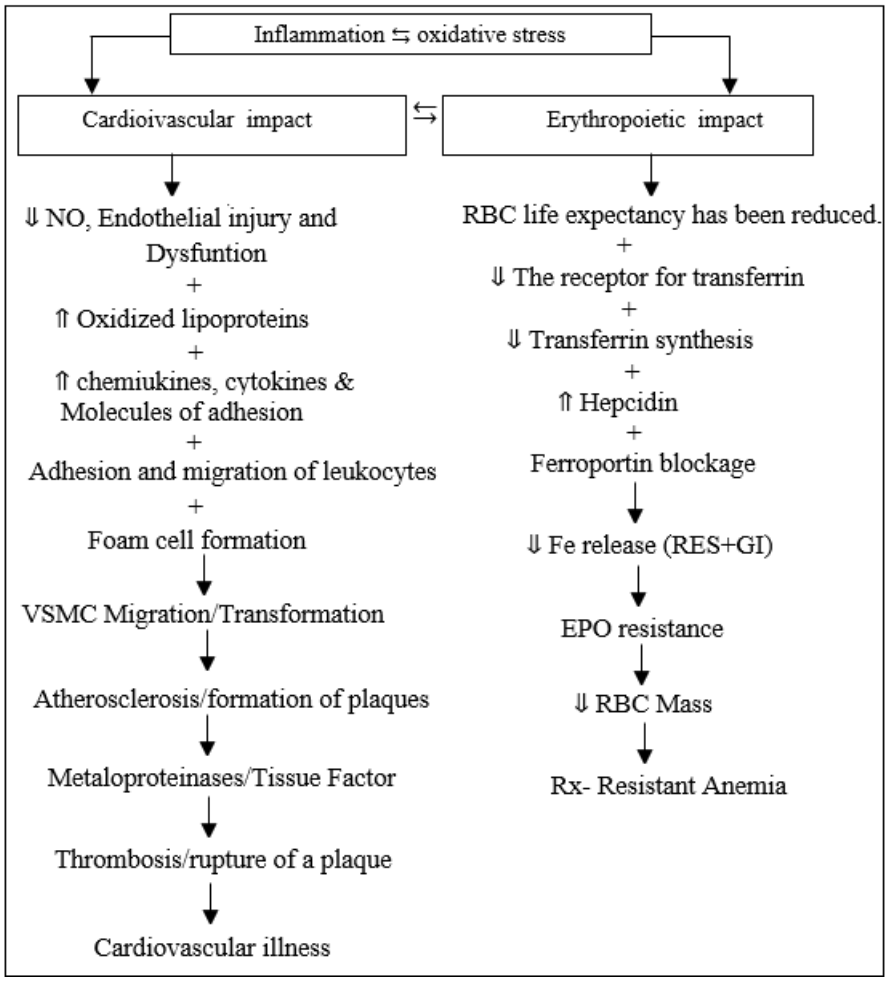

Figure 1: Figure illustrating the relationship between oxidative stress and inflammation and how they can both lead to cardiovascular disease and EPO - resistant anaemia

Correction of anaemia versus medication toxicity as the root of negative effects: -

Observational studies indicating a link between the severity of anaemia and poor outcomes prompted a slew of randomised clinical trials examining the possibility that correcting anaemia may improve cardiovascular outcomes. [**25, 26, 27]**. Contrary to expectations, patients who were randomly assigned to groups with normal Hb either did not improve from treatment or experienced worse cardiovascular and other outcomes. These results were interpreted to mean that treating anaemia could be harmful in those with CKD. Notably, only a small proportion of patients were assigned to the high - Hb groups. (21% in CHOIR and 38% in CREATE) achieved the anticipated target despite receiving high doses of EPO and iron [**26, 27]** This suggests that a significant proportion of the study populations had severe treatment - resistant anaemia, most likely due to significant oxidative stress and inflammation. Outside of erythropoietin, EPO and iron have a variety of other effects that are beneficial at physiological levels but harmful at high concentrations. As a result, increased morbidity and mortality in patients randomised to higher Hb objectives in clinical trials may be attributable to EPO and/or iron excess rather than anaemia correction, which was seldom even accomplished in the majority of patients**.** The finding that a subset of patients whose haemoglobin levels could be normalised performed significantly better [**25]** and the discovery that CKD patients (such as those with polycystic kidney disease) who maintain

normal Hb levels without EPO therapy typically perform as well as or better than their anaemic counterparts. **[28]** support this claim. It is noteworthy that in the randomised clinical trials of anaemia correction, Patients in the normal or near - normal Hb groups received a median dose of EPO that was two to three times that of patients in the lower Hb groups. **[25, 26, 27]**. Furthermore, further analysis of the CHOIR study's data revealed that failure to meet a target Hb and a high EPO dose were both significantly linked to a higher risk of the study's main endpoints, such as mortality, myocardial infarction, congestive heart failure, or stroke. **[24]**. These findings point to a possible role for the non - erythropoietic effects of high doses of EPO (and possibly iron), which are briefly discussed below.

EPO's non - erythropoietic effects

Endothelial cells, vascular smooth muscle cells, cardiomyocytes, skeletal myoblasts, neurons, liver stromal cells, macrophages, kidney, and other organs all express EPO receptors, as do the retina, placenta, and various cancerous cell types. The activation of these receptors is responsible for EPO's numerous nonerythropoietic effects, including angiogenic, anti - apoptotic, vaso - regulatory, hemostatic, and other actions that are extremely beneficial at physiological levels but potentially deleterious at high EPO levels/doses. Figure 2 summarises some of the Both positive and negative EPO actions have effects on the cardiovascular system, blood coagulation, and the kidney.

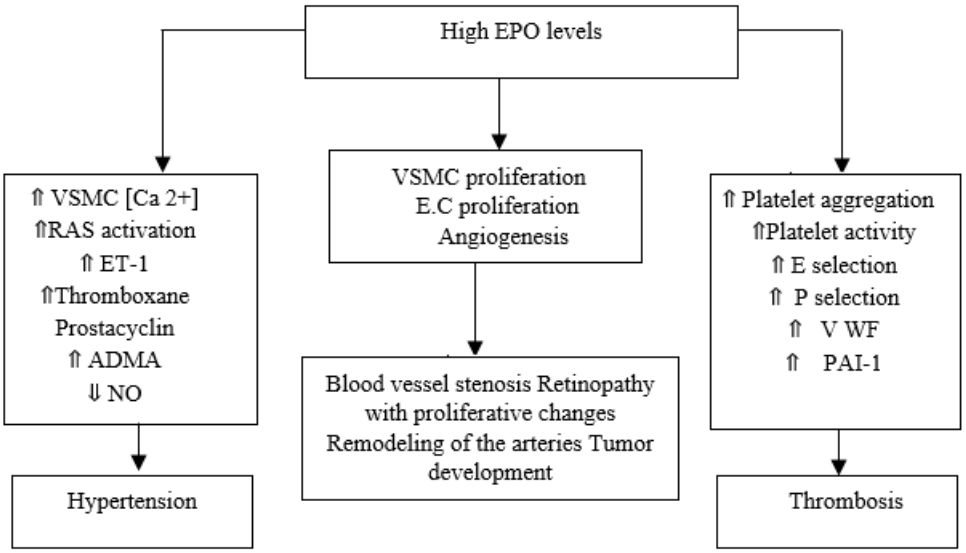

Figure 2: Figure showing the non - erythropoietic effects of EPO that could promote the formation of tumours, thrombosis, vascular remodelling, diabetic proliferative retinopathy, hypertension, and hemodialysis blood access stenosis.

The impact of EPO on blood pressure: -

Experimental animals and CKD patients both develop hypertension after receiving EPO [**30, 31]**. Because it occurs in both iron - deficient and iron - sufficient CKD mice, despite persistent anaemia in the former, EPO - induced hypertension is unrelated to its erythropoietic effect. **[32, 33]**. Additionally, arterial pressure is not increased by treating anaemia with numerous red blood cell transfusions in CKD animals or iron replacement therapy in iron - deficient CKD patients [**32, 33, 34]**. These findings offer unquestionable proof that the medication itself, not changes in erythrocyte mass, is what causes EPO - induced hypertension. The processes through which EPO affects the cardiovascular system and arterial pressure have been are briefly outlined here and have been reviewed in full elsewhere [**30, 31]**:

1) Cytosolic ionised calcium concentration ([Ca2+]i) – In vascular smooth muscle cells (VSMC), EPO increases cytosolic [Ca2+]i and calcium reserves in the sarcoplasm. [**32, 33]**. These occurrences, in turn, increase arterial pressure and systemic vascular resistance while decreasing the vasodilator response to nitric oxide (NO).
2) Endothelin - 1 (ET - 1): Patients on dialysis who received EPO had higher plasma ET - 1 levels. **[35]**, ET - 1 levels are higher in isolated vessels and cultured endothelial cells. **[35, 36, 37]**. Vasoconstriction, ROS production, and hypertension may all be promoted as a result of increased ET - 1 production.
3) EPO increases the expression of several angiotensin II - responsive factors, including TGF - beta, insulin - like growth factor - II, epidermal growth factor, c - fos, and platelet - derived growth factor, in cultured VSMC and upregulates the expression of renin, angiotensinogen, and angiotensin receptor. **[38, 39]**. It's worth noting that homozygosity for the T allele of the angiotensinogen gene is associated with EPO - induced hypertension in CKD patients. **[40]**. Last but not least, EPO therapy hastens renal disease progression in five of six nephrectomized rats that react well to AT1 receptor blockage and ACE inhibition [**41]**.
4) In cultured human endothelial cells and in the vascular tissue of CKD rats [**42, 43]** PGF2 and thromboxane are increased by prostaglandins - EPO, while prostacyclin is decreased.

Long - term EPO treatment can promote hypertension and vascular damage by increasing VSMC [Ca2+]i, activating tissue RAS, increasing endothelin - 1 synthesis, and increasing the thromboxane/prostacyclin ratio in the vascular tissue. EPO medication, on the other hand, reduces the vulnerability of ESRD patients to intradialytic hypotension by increasing vascular tone. This can then make it easier to manage hypervolemia while receiving hemodialysis via ultrafiltration.

EPO's effects on the platelet and coagulation systems: -
EPO therapy significantly increases platelet count in ESRD patients with platelet counts of 150 000/mm3 (regardless of its impact on hematocrit) **[44]**. This phenomenon results from thrombopoietin's thrombopoietic activity being amplified by EPO. EPO also increases platelet responsiveness, which may lead to a pro - thrombotic state, by increasing intracellular calcium reserves and speeding up the rise in cytosolic [Ca2+]i after activation. **[45]**. EPO can also improve blood coagulation by promoting the production of E selectin, P selectin, von Willebrand factor (vWF), and plasminogen activator inhibitor - 1 via pathways involved in tissue factor expression. **[46, 47, 48, 49]**. Therefore, despite the fact that EPO can correct uremic platelet dysfunction being advantageous, large doses of EPO have been linked to thrombotic problems in CKD and cancer patients [**50]**.

Effects of EPO on the kidney
Functional EPO receptors are expressed by the kidney's vascular and nonvascular parts [**51]**. When the EPO receptor is activated, apoptosis is prevented and cell survival is increased. Numerous studies have shown that EPO therapy can improve kidney function and structure recovery and reduce apoptotic cell death in many models of acute kidney damage caused by ischemia - reperfusion or nephrotoxic chemicals. **[52, 53, 54]**. EPO has also been shown to have anti - apoptotic properties in vitro in cultured podocytes. [**55]**.

The ability of EPO to increase platelet synthesis, platelet reactivity, and endothelial cell expression of tissue factor and other pro - thrombotic molecules, as previously described, counteracts EPO's beneficial effect on cell survival in acute injury models. The latter events can aggravate injury and impede healing by promoting microvascular thrombosis and the production of pro - fibrotic, pro - inflammatory mediators from activated platelets and coagulation proteins like thrombin. This is especially likely when endothelial dysfunction and damage coexist with parenchymal injury, which is common in many types of acute and chronic renal illness, hypertension, and cardiovascular problems.

According to some theories, the anaemic condition's intrinsic restriction of oxygen delivery can hasten apoptotic cell death, promote fibrosis, and thus aid in the progression of chronic kidney or other organ illnesses. If this is the case, treating anaemia should be beneficial because it will prevent the condition from worsening. Surprisingly, a few studies have shown that administering modest sub - erythropoietic doses of EPO may slow the progression of renal disease in diabetic db/db mice and rats with reduced renal mass. **[56, 57]**. Similar to this, a group of CKD patients' partial anaemia improvement with modest doses of EPO was observed to delay the rate of development of ESRD [**58].** Large doses of EPO, on the other hand, have been shown repeatedly to hasten the development of renal illness in animals with renal mass loss. [**56, 59]**, diabetes [**57],** and glomerulonephritis caused by antibasement membrane antibodies [**55**]. Similar to this, Recent large randomised clinical trials discovered a significant trend for patients assigned to high - Hb groups to develop ESRD, necessitating renal replacement treatment. The recent discovery of a strong link between the development of severe diabetic proliferative retinopathy and nephropathy and an EPO gene promoter polymorphism that causes increased EPO production **[60]** reinforces the idea that high levels of EPO contribute to the advancement of renal disease.

As a result, high EPO doses may hasten the progression of chronic renal disease, Despite the fact that physiological levels of EPO provide significant benefits via a variety of non - erythropoietic and erythropoietic effects. This finding is supported by evidence from randomised clinical trials and data collected from experimental animals. The most likely explanation for these effects is that pre - existing inflammation and endothelial dysfunction exacerbate EPO's pleotropic effects.

Non - erythropoietic effects of EPO could contribute to poor outcomes. Unfavorable outcomes in clinical studies of anaemia correction in CKD populations may be due to the unanticipated consequences of high EPO dosages, as briefly mentioned above. It is important to note that resistance to EPO's erythropoietic effects is not always followed by resistance to those effects that are not erythropoietic. This is well demonstrated by the fact that recombinant EPO can increase calcium signalling Despite the former's persistent anaemia and the latter's cure, both iron - deficient and iron - sufficient CKD rats develop severe hypertension. [31, 32]. Therefore, in individuals with EPO - resistant anaemia, increasing the dose of EPO can have unfavourable effects resulting from its non - erythropoietic actions. It is worth noting that CDK causes a significant decrease in erythrocyte lifespan that is unaffected by current therapies.

To maintain normal erythrocyte mass in patients with advanced CKD, higher levels of sustained erythropoiesis are required than in healthy people, especially when significant oxidative stress and inflammation are present. As a result, aggressive therapies to maintain normal or nearly normal erythrocyte mass in these patients frequently necessitate high doses of EPO, which can lead to medication toxicity and overdose.

2. Conclusion

Treating anemia with ESA in CKD patients resulted into improved function, exercise tolerance, decreased morbidity, increased cognitive function and overall quality of life However high dose of epoetin exerts toxic effect, thus need to follow guidelines strictly. Administration of ferric gluconate is effective in anemic dialysis patients receiving adequate epoetin dosage and increases HB faster and higher. Thus, Hb targets setting also plays an important role. Increasing intensity of dialysis in anemic patients results into significantly increase in hematocrit. Various strategies to improve outcomes include clinical practice guidelines for CKD and managing HTN, Dyslipidemia, Bone disease, Nutrition and CVD in CKD patients. This can be achieved only by continuous monitoring.

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