



ERYTHROPOIETIN HYPORESPONSIVENESS: ITS RISKFACTORS

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Abstract: Since anaemia is a common consequence of CKD., this study was designed to learn more about it (CKD). Higher likelihood of hospitalisation has been associated with anaemia. Chronic renal impairment (CKD) morbidity and fatality are both accelerated by anaemia. Treatment with erythropoietin (EPO) for anaemia was very helpful for several individuals but not for others. Experimental as well as clinical data show that a number of factors contribute to an inadequate response to EPO therapy. Those who have chronic kidney disease (CKD) frequently experience hyporesponsiveness to erythropoietin stimulating drugs (ESA) and fluctuating Hb (haemoglobin) levels., and this study shows that functional iron deficiency (FID), chronic inflammation, renin-angiotensin system inhibitors (RASIs), a lack of L-carnitine, and malnutrition are the primary causes of anaemia. **CONCLUSION:** The findings of investigations have shown that functional iron deficiency (FID), chronic inflammation, renin-angiotensin system inhibitors, a lack of L-carnitine, and malnutrition Could be a factor in the Hb level fluctuation and ESA hyporesponsiveness that are regularly seen in Ckd.

Index Terms - Erythropoietin hyporesponsiveness, iron deficiency, inflammation, L carnitine, ACE inhibitors, malnutrition.

I. INTRODUCTION

No matter the cause or even a GFR < 60 mL/min/1.73 m² or less for 3 months, or renal injury or longer constitutes (CKD).¹¹ The frequency and occurrence of chronic kidney disease (CKD) are both on the rise, with an estimated 850 million people around the world thought to have the disease due to various causes.³ Amidst advances in medicine and the availability of dialysis techniques, it remains the sixth most common fatality worldwide, accounting for 2.4 million deaths on an annual basis.³ It is estimated that in country like India, the prevalence is closer to 17%, making the situation even more dire.³

Dialysis, is a medical process that removes metabolic byproducts from the blood and restores proper electrolyte balance.⁶ Dialysis machines and dialyzers are used to treat patients with chronic renal failure.⁶

A known complication of persistent kidney failure is anaemia.¹² Severe kidney illness patients, anaemia is related with a higher risk of hospitalisation, mental impairment, a reduced standard of living, and serious cardiovascular events.¹² Mortality and morbidity rates in people with chronic kidney disease are higher when anaemia is present. ² The root cause of anaemia in CKD patients is multifaceted.¹²

Care with erythropoietin (EPO) for anaemia was very helpful for some patient populations, but not for others. According to both experimental and clinical evidence ², poor response to EPO therapeutic interventions can be caused by a number of factor. ²

According to the Kidney Disease Outcomes Quality Initiative (NKF KDOQI), hyporesponsiveness to EPO is defined that possessing at a minimum one of the following characteristics:

Possible outcomes include needing a much higher dose of EPO to keep the same haemoglobin level, having the haemoglobin level drop significantly while the EPO dose remains the same, or failing to reach >11 g/dl despite receiving a dose of EPO equal to EPO >500 IU/kg/week. ⁹

Hyporesponsiveness to ESA treatment is measured using the ESA hyporesponsiveness index (EHRI).⁸

The EHRI is calculated by dividing the ESA dosages per kilogram body weight per week (IU/kg/W) by the haemoglobin level (g/dl).⁸

The most common causes of anaemia are low levels of erythropoietin (EPO), functional iron deficiency (FID), systemic inflammatory, angiotensinogen system inhibitors, low levels of L-carnitine, and undernourishment.¹²

ESA Hyporesponsiveness can also be caused by inadequate dialysis, a haemodialysis catheter, diabetic neuropathy, periodontitis, contaminated dialysate, neoplasms, other (rare), stem cells diseases, hyper parathyroidism, myelosuppressive prescription drugs, hypersplenism, hemolytic anemia, pure red blood cell aplasia, and unknown (33%).⁵

Erythropoietin hyporesponsiveness is brought on by a variety of processes, including

DEFICIENCY OF IRON

Dysregulation of iron homeostasis and erythropoiesis is common in individuals who have persistent kidney disease (CKD), and this often results in anaemia.¹ Patients with HD who do not respond to ESA therapy Resistance to ESA therapy could be attributed to an array of factors, including a lack of iron in the body, frequent blood tests, occult blood loss from the gastrointestinal tract, elevated hepcidin levels, Standard diagnostic testing and loss of blood from the HD extracorporeal loop.⁸

Having a high blood ferritin content (>800 ng/mL) 20 because to inflammation could mask the presence of an iron deficiency.⁸ Hepcidin is a critical regulator of iron availability and is responsible for iron accumulation during iron repletion.⁸

Decreased hepcidin levels promote iron accessibility for erythropoiesis in the presence of hypoxia and/or iron shortage.⁸ Pathological conditions are prevalent among individuals with CKD, and increased hepcidin production under these conditions is associated with an

increased risk of kidney failure due to decreased hepcidin excretion by the kidneys.⁸ rise in ferritin levels, decreased iron content and iron-binding ability, and an abundant supplying circulating hepcidin six to nine times higher than normal, all of which are exacerbated by inflammatory conditions, are suggestive reticuloendothelial iron absorption and insufficient serum iron to allow red blood cell production.⁸ Erythropoiesis suffers as a result of a decrease in the quantity of iron available due to decreased Gut iron uptake and reticulo - endothelial cell iron release.⁸

INFLAMMATION

Hyporesponsiveness was also significantly associated with inflammatory markers like CPR.⁸ Another method in which inflammation influences erythropoiesis is by preventing hypoxia from inducing erythropoiesis-stimulating EPO synthesis in Hep3B cells.² One amongst inflammation's key routes to promoting anaemia is through its effect on iron homeostasis.² The inflammatory state may have a role in the development of anaemia through a mechanism that may involve hepcidin, which has an impact on iron in body by attaching to ferroportin, a cellular iron transporter. Thus, autophosphorylation, internalisation, ubiquitinylation, and lysosomal destruction of ferroportin occur.² Reduced iron absorption from the duodenal enterocytes and decreased iron release from phagocytes into the vascular endothelium system as a result of this ultimately lead to hypoferrremia.²

About 30%-50% of ESRD patients may have high CRP and pro-inflammatory interleukins such as IL-1, IL-6, and tumour necrosis factor thresholds (TNF-), according to clinical signs of an active acute inflammation.²

Persistent lower-grade infection in renal failure patients has been linked to oxidative stress, viral issues, poor elimination of cytokines, and variables associated with dialysis.²

THE ACE INHIBITORS

Since ACE inhibitors have beneficial effects on the heart, they are commonly prescribed to patients with chronic kidney disease (CKD).⁷

The renin-angiotensin system regulates blood pressure through regulating plasma volume and vascular resistance. The enzyme angiotensin-converting enzyme (ACE) encourages activation and erythroid progenitor cell conversion. The growth factor angiotensin II (AT II) increases erythropoietin secretion from erythroid progenitor cells (EPO). Serum erythropoietin concentration is reduced alongside a decrease in blood AT II level due to ACEi medication.⁷ Kidney circulation is lowered because ACE inhibitors dilate efferent and afferent arterioles and decrease erythropoietin production.⁷ Care should be taken while administering ACE inhibitors to HD patients receiving ESA.⁷ Finding the optimal dose of ACE inhibitors to ensure cardiac function without interfering with erythropoiesis is a priority.⁷

L CARNITINE

Parenchymal damage to the kidney prevents the body from producing its own L-carnitine supply.³ L-carnitine does have a disastrous impact on the red blood cells of a patient and serum lipids, that could lead to the participant's premature death.³ People who have chronic kidney disease will undoubtedly lose the easily dialyzable molecule L-carnitine during the process of hemodialysate clearance.³ It's an important intermediary step in fat metabolism.³ Fatty acids with a long chain of carbon atoms are transported through the mitochondria the amino acid arylcarnitine and oxidised there.³

Moreover, it neutralises free radicals and alters the concentration of coenzyme A.³ Individuals with chronic kidney failure are protected from inflammation and the resulting oxidative damage due to the physiological significance of this biomolecule.³ By doing so, steady haemoglobin levels can be maintained a somewhat lower EPO dosage than in other dialysis patients who do never routinely take L-carnitine.³

L-carnitine, particularly in its acylated form, is able to activate lecithin cholesterol acyl transferase, an enzyme that lowers levels of low-density lipoprotein and very low-density lipoprotein levels while increasing high-density lipoprotein levels (HDL).³ Loss of L-carnitine and the biological responses it has can have a negative impact on the health of patients who have chronic kidney disease (CKD).³

MALNUTRITION

Individuals who are undergoing haemodialysis are need to follow certain nutritional recommendations requirements. It is proposed that these patients cut back on the amount of fluids they consume and steer clear of meals that are high in phosphate, potassium, and sodium.¹³ Patients often have trouble getting enough protein and calories, which makes it difficult for them to achieve these needs.¹³ Also, depression is common among these patients, further contributing to an already significant decrease in appetite.¹³ Patients receiving replacement kidney therapy particularly vulnerable to developing nutritional status difficulties due to the above obstacles.¹³ However, the patient has no control over certain variables, such as the loss of protein residues and iron after every haemodialysis.¹³ If nutritional condition were described in this manner, it would give the impression that the only thing that is required to cause clinical improvement is a change in diet.¹³

Type II malnutrition is characterised by inflammation's role in the aetiology and progression of the condition, making nutritional intervention futile. Another name for this condition is the MIA (undernourishment, infection, and arteriosclerosis) syndrome (malnourishment, inflammation, cachexia). In addition to "minimally invasive cancer," "MIA," and "MIC" are all terms for this condition.¹³

OTHERS

Although erythropoietin treatment is well tolerated by the vast majority of patients, a small number of those treated will develop antibodies that will counteract the effects of the natural and synthetic proteins used in the treatment.¹⁹ Epoetin alfa administered subcutaneously has been linked to the formation of antibodies in the majority of cases.¹⁹ Transfusion dependence and PRCA (pure red cell aplasia) anaemia are potentially lethal conditions associated with the formation of anti-erythropoietin (anti-EPO) antibodies. A deficiency in red blood cells is a hallmark of both of these disorders.¹⁹ New research had also demonstrated that anti-EPO antibodies driven PRCA is a serious but uncommon side effect that really can happen in rHuEPO-treated Ckd.. Responses of rHuEPO to the same genetic variation can be somewhat different depending on the individual.¹⁹

The Central Venous Catheter has the potential to create chronic inflammation and infection, which can result in the generation of inflammatory cytokines and partially limit erythropoiesis. This is because of the catheter's proximity to the blood vessel that contains the red blood cells.²⁰

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