



Erythropoietin Stimulating agents Responsiveness in Chronic Kidney Disease Patients on Maintenance Haemodialysis

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ABSTRACT

The condition in which the kidneys deteriorate is known as chronic kidney disease (CKD) where it fails to remove the excess fluid and waste from the blood. As damage to the kidney progresses, there is diminished production of endogenous erythropoietin by the kidneys, resulting in anaemia. So, the patients are supplemented with erythropoietin stimulating agents (ESAs) for maintaining haemoglobin at normal levels. To assess erythropoietin stimulating agents' response to Erythropoietin Resistance Index (ERI) and to determine predictors for its resistance in chronic kidney disease patients undergoing maintenance haemodialysis. Observational Prospective research involving 180 patients receiving regular haemodialysis for chronic renal disease was carried out from August 2022 to January 2023. Of 180 patients involved in the study, 160 patients have shown hyporesponsiveness and 20 patients responded well to ESA's. Among 160, 102(63.75%) were males and 58(36.25%) in females. Distribution of comorbidities among 160 was: Hypertension- 96(60%), Diabetes Mellitus 26(16.25%) and Mineral Bone Disorder associated with CKD 38(23.75%). Risk factors found were Serum Ferritin (60%), Serum Albumin (52.5%), Parathormone (36%), Serum Calcium (52.52%), Serum Phosphorus (43%), use of ACE i's/ARB's (62.5%), Statins (21.2%), BMI(47.5%). Erythropoietin hyporesponsiveness has occurred due to various like low BMI, statins, angiotensin converting enzyme inhibitors or angiotensin receptor blockers usage, high serum ferritin, less serum albumin, increased parathormone, less serum calcium, serum phosphorus levels.

KEY WORDS: Hyporesponsiveness, Chronic Kidney Disease, Erythropoietin, Angiotensin Receptor Blockers, Angiotensin Converting Enzyme inhibitors.

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INTRODUCTION

Chronic renal disease (CRD) is defined as the kidneys failure to eliminate waste and extra fluid from the bloodstream as a result of hypertension, diabetes, hypercholesterolemia, and ageing. Less than 60ml/min/1.73m² is the estimated glomerular filtration rate, which indicates chronic kidney disease, as per the National Kidney Foundation.[1]

For all the subpopulations, the ideal course of treatment for renal anaemia has not yet been thoroughly determined.[2] To help clinicians, diagnose and treat anaemia in CKD patients, a number of practice guidelines have been developed.[2]

Since the 1990s, it has been well documented that treating chronic kidney disease anaemia with erythropoietin stimulating agents (ESAs)[2] like recombinant human erythropoietin (rHuEPO) and iron has the primary goal of decreasing renal anaemia-related symptoms and preventing RBC transfusions.[3] Erythropoietin was created to supplement the lack of endogenous erythropoietin (EPO) caused by the progression of CKD.[4]

Guidelines in the year 2012, from KDIGO (kidney disease: Improving Global Outcomes advised against using erythropoietin stimulating agents to keep haemoglobin levels in adults with CKD over 11.5 g/dL.[5] However, many ESRD patients show diminished responses to ESAs.[6] Some people have erythropoietin (EPO) hyporesponsiveness or EPO resistance, which refers to patients who do not respond well to EPO.[3] The effectiveness of erythropoietin therapy can be affected by a variety of circumstances, and 5-10% of patients show clear signs of resistance to the drug.[4]

The National Kidney Foundation's (NKF's) Kidney Disease Outcomes Quality Initiative (KDOQI) has developed a concept for ESA hyporesponsiveness/resistance to describe when patients are unable to reach

or maintain haemoglobin (Hb) levels while receiving greater than typical dosages of ESA. The influences have been established for a long time.[7]

The phrase erythropoietin resistance refers to the inability to reach the required haemoglobin level despite the use of larger than usual doses of erythropoietin and ongoing treatment to greater doses of erythropoietin to maintain the level that has been attained.[3] Because it results in the unfulfilled Hb objective, raises the expense of therapy, and is linked to unfavourable outcomes, ESA hyporesponsiveness is a therapeutic concern. ESA hyporesponsiveness results in greater blood transfusions with the danger of allosensitization for forthcoming kidney transplants; whose only benefit of ESAs acknowledged by the United States food and drug administration is the minimization of transfusions.[8]

In order to assess how the body reacts to Erythropoietin (EPO) one useful metric is the Erythropoietin Resistance Index (ERI).[9]

The erythropoietin resistance index (ERI), derived from the dose of erythropoietin and haemoglobin level, is a significant evaluation metric for EPO responsiveness.[3]

In order to calculate ERI, we divide the ESA dose per kilogram of body weight per week (IU/kg/W) by the Hb range (grams/decilitre).[6]

The reasons for ESA hyporesponsiveness are not well known, however, they entail the number of factors, including: Iron deficiency (serum ferritin <300 ng/dL)[8], Inflammation [14], Malnutrition, inadequate dialysis, Statins [7], Age and Gender [4], Low serum albumin [7], Infections, Cancer, Blood loss, Vitamin B₁₂ or folate deficiencies [4], Lack of L-carnitine, Unknown (approximately one-third) [8]

The responsiveness to EPO is significantly influenced by age and gender. The burden of inflammation, starvation, and blood loss increases with advancing age. Adult females may require more EPO than adult males due to androgenic stimulation of male erythropoiesis.

Similarly, despite CKD's hypogonadotropic impact. Women who can still have menstrual periods frequently need more EPO.[4]

Due to the increase in the inflammatory state in CKD there is iron-restricted erythropoiesis and high serum levels of hepcidin-25 and an increase in C-reactive protein and interleukin-6.[10] PTH is excessively secreted, which causes bone marrow fibrosis and indirectly interferes with erythropoiesis; instead, EPO is produced as a result of bone marrow fibrosis and a uremic environment.[11] In HD patients, the nutritional condition is linked to EPO resistance, mostly due to the relationship between inflammation and malnutrition.[13] Hematologic reaction to ESA erythropoiesis is decreased by blocking the renin-angiotensin system and ACE inhibition and thus decreases ESA responsiveness. Additionally, it is discovered that low calcium readings are independent predictors of an insufficient response to erythropoietin stimulating agents.[13]

MATERIAL AND METHODS

This is a prospective observational study that aims to assess the responsiveness of erythropoietin stimulating agents and predictive factors responsible for its resistance in patients undergoing maintenance haemodialysis with chronic kidney disease from the month of August 2022 to January 2023. For calculating the different laboratory parameters, the methods used are Haemoglobin was calculated by SLS haemoglobin method, Serum Calcium was calculated by Colorimetric O-cresolphthalein Complexone (CPC AMP) method, Serum Phosphorous was calculated by Colorimetry without precipitation, Serum Creatinine by Jaffe's kinetic test, Blood Urea Nitrogen (BUN) by Urease GLDH, Serum Albumin by Bromocresol purple, Serum Ferritin by Immunoturbidimetric method

Statistical analysis: All data were subjected and variables were calculated using frequency and percentages.

RESULTS AND DISCUSSION

Erythropoietin resistance is calculated by using the formula: Mean weekly weight-adjusted dose (U/Kg per week) divided by the average three-month haemoglobin level (g/dL). 160 of the 180 patients were found to be hyporesponsive to erythropoiesis-stimulating agents.

Various research has evaluated the different lab parameters like inflammation, serum ferritin, parathormone levels, infection, dialysis inadequacy, Kt/v, serum albumin etc., to assess the erythropoietin (EPO) hyporesponsiveness. [8,14,7,4]

The risk factors causing erythropoietin hyporesponsiveness discussed in this study are: Malnutrition, Iron deficiency, Parathormone levels, Serum Albumin, Serum Calcium, Serum Phosphorous, usage of Statins and ACE inhibitors/ ARB's (Angiotensin-Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers)

Out of 160 hyporesponsive patients, gender-wise distribution of erythropoietin (EPO) resistance showed that average age was 41.7 years and weight 54.54kgs (refer: table 1) males were 63.75% and females 36.25%. (refer: table 2)

It was found that comorbidities associated with chronic kidney disease (CKD) among Hyporesponders are hypertension 60%, mineral bone disorder 23.75%, and diabetes mellitus 16.25%.(refer table 3 figure 2)

Table 4 shows the Percentage of risk factors resulting in erythropoietin hyporesponsiveness are: 47.5% were found to be malnutrition with Low Body Mass Index, 52.5% with low Serum Albumin level (due to Nutritional Deficiency); 60% with increased Serum Ferritin; 36% with increased Parathormone level; 52.5% were having decreased Serum Calcium; 43% with elevated Phosphorous levels; 62.5% were on ACE inhibitors/ ARB'S and 21.2% were using Statins.

It concluded that, the responsiveness of Erythropoietin Stimulating agents (ESA's) was determined by using the Erythropoietin Resistance Index (ERI). Most of the patients were found to be Hyporesponsive due to various risk factors like an increase in the levels of Serum Ferritin, Parathormone (PTH), Serum Phosphorous, and a decrease in Serum Albumin (hypoalbuminemia), Serum Calcium, low Body Mass Index (BMI) and usage of drugs like Statins, and Angiotensin Converting Enzyme Inhibitor's (ACE's) or Angiotensin Receptor Blockers (ARB's). Due to malnutrition, increased serum ferritin levels, and concomitant use of drugs (like Statins, ACE i's or ARB's) causing high erythropoietin (EPO) resistance resulting in anaemia. EHRI appears to be a valuable tool for determining the clinical status of patients and is simple to compute in daily practice.

Table 1: DEMOGRAPHIC DATA

The average age of 160 patients is displayed in the table below.

No. of patients (160)	Mean
Age	41.7Years
Weight	54.54Kgs

The table depicts the mean age of 160 patients of both genders (male and female) is 41.7 years and the second parameter is the average weight of 160 patients is 54.54kgs.

Table 2: Occurrence of erythropoietin resistance in CKD in both genders.

GENDER	N=160	N%
MALE	102(102/160)	63.75%
FEMALE	58(58/160)	36.25%

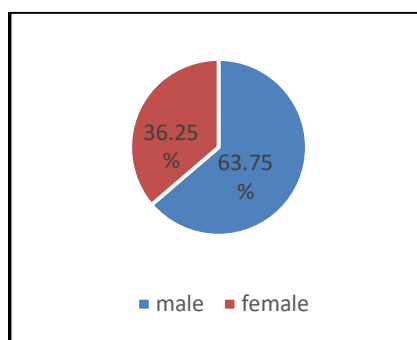


Figure 1: Pie chart depicts the occurrence of hyporesponsiveness in males (63.75%) and females (36.25%).

Table 3: Comorbidities associated with chronic kidney disease (CKD) among hyporesponders

COMORBIDITIES	N	N%
HYPERTENSION	96(96/160)	60%
MINERAL BONE DISORDER	38(38/160)	23.75%
DIABETES MELLITUS	26(26/160)	16.25%

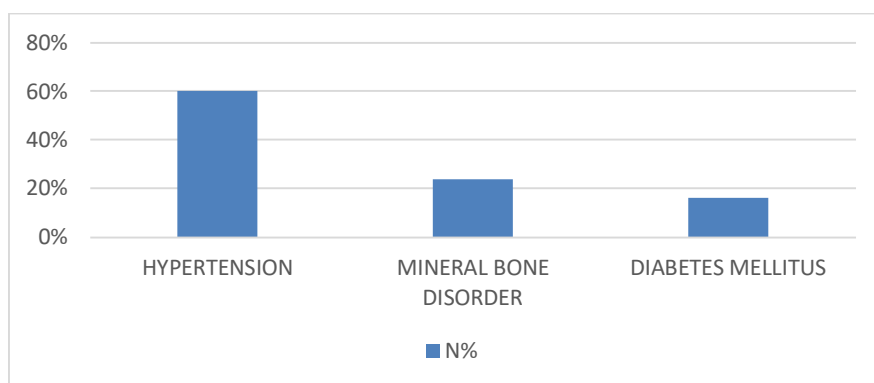


Figure 2: Graphical representation of comorbidities associated with chronic kidney disease (CKD). Out of 160 hyporesponders, Hypertension patients were accounting for 96(60%); Mineral bone disorder associated with CKD was 23.75%; Diabetes Mellitus was 16.25

Table 4: Risk factors contributing to erythropoietin resistance in hyporesponders

PARAMETERS	N	PERCENTAGE
SERUM FERRETIN	96 (96/160)	60%
SERUM ALBUMIN	84 (84/160)	52.5%
PARATHHARMONE	58 (58/160)	36%
SERUM CALCIUM	84 (84/160)	52.5%
SERUM PHOSPHORUS	70 (70/160)	43%
ACE'S / ARB'S	100 (100/160)	62.5%
STATINS	34 (34/160)	21,2%
BMI	76 (76/160)	47.5%

ACE i's: Angiotensin Converting Enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; BMI: Body Mass Index; N: frequency; N%: frequency %.

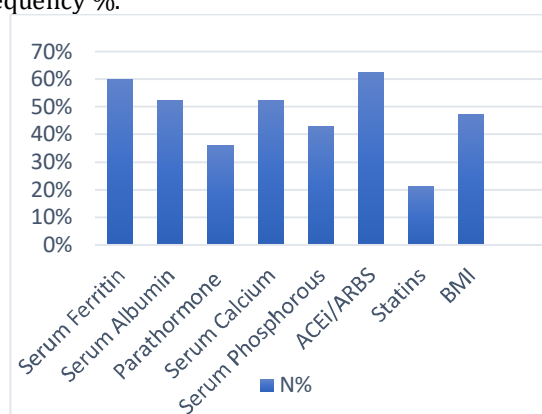


Figure 3: The graph illustrates the percentage of risk factors associated with erythropoietin hyporesponsiveness.

The percentage of serum ferritin=60%; serum albumin=52.5%; parathormone levels=36%; serum calcium=52.52%; serum phosphorus=43%; use of ACE i's/ARB's=62.5%; statins use=21.2%; percentage of Body Mass Index is 47.5%

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Conflict of interest

The authors declare that there is no conflict of interest.

Authors Contribution

Every one in the group contributed equally.

Ethics statement

It was approved by Institutional Ethics Committee of Malla Reddy Institute Of Pharmaceutical Sciences,

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