

REVIEW ARTICLE

Use of Recombinant Human Erythropoietin in Renal Anemia in Children

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Abstract:

Erythropoietin is a hormone highly effective as like as natural erythropoietin to maintain target hemoglobin and hematocrit level in renal anemia. Its advantage over blood transfusion has been proved by improving the quality of life and decreasing morbidity and mortality in ESRD patients. Effectiveness of r-erythropoietin depends on absences of infection, inflammation and vitamin deficiency and iron status. Iron supplementation is needed before r-erythropoietin administration and sub-cutaneous route is better in renal anemia because of slow and sustained releases of r-erythropoietin from the site of administration.

Target hemoglobin level is 11-12.5 gm/dl and hematocrit is 33% which can be achieved by this hormone therapy.

Key wards- Recombinant erythropoietin, renal anemia, end stage renal disease.

[BSMMU J 2009; 2(1): 50-53]

Introduction

For many years anaemia has been recognized as one of the commonest manifestation of end stage renal diseases (ESRD) both in children and adult, which contribute significant morbidity, and mortality in renal patients¹.

In 1836 Richard Bright was first noticed the association of anemia with renal failure. In case of renal failure anemia became apparent, when glomerular filtration rate (GFR) is less than 30 ml /min/1.73m² and gradually progresses in a near linear fashion².

Initially, primary methods for treating renal anemia was blood transfusion but as it was associated with transfusion related side effects such as viral infections, iron overload, sensitization to antigen and short life span of RBC³.

At present, it is established that like many other contributing factors, due to deficiency of hormone Erythropoietin is the initial stimulating factors for effective erythropoiesis in the bone marrow which resulted in the development of anemia in renal failure⁴.

So, use of r-human erythropoietin stimulates the production of newer red cell in the bone marrow resulting increase hemoglobin concentration that can reduce blood transfusion related side effects.

In 1986, the clinical trial of the use of recombinant human EPO (r HUEPO) in renal anaemia was being reported. In

keeping with this concept of anaemia of ESRF now the r-HUEPO is used routinely.

It is also used in case of chemotherapy induced anemia, inflammation, premature and very low birth weight baby, thalassemia etc.

Now, recombinant human EPO (r HUEPO) is available in Bangladesh also, in different formulation and doses. Over 90% of chronic renal diseases, patients with or without dialysis have persistent anemia and need treatment for that conditions.

An analysis of safety data accumulated on 3697 patients with renal anemia who received erythropoietin evidenced the benefit of the treatment while remaining highly tolerable. So, anemia due to renal diseases treated with r HUEPO has proved to be a viable alternative to transfusion therapy.

Source of Erythropoietin

The exact formation site is not known. But the primary site of erythropoietin formation in the kidneys peritubular interstitial fibroblast of the cortex, medulla, and proximal tubular cells and to a lesser amount from liver. Secretion of erythropoietin controlled by a gene presence on chromosome 7.

Normal blood level of erythropoietin

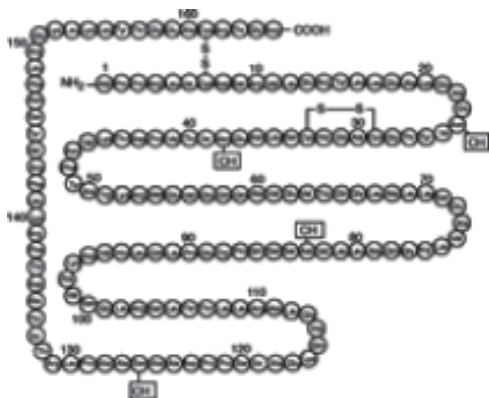
The normal serum level of Erythropoietin 10-12 mU/ml. this level may increase up to 1000 folds when renal function is normal in cases of hypoxia and anemia^{4,5}. But in case

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of impaired renal function this physiological level of erythropoietin is not sufficient to stimulate normal erythropoiesis.

Structure of erythropoietin

It contains 193 amino acids of which the first 27 are cleaved during secretion and also contain 4 carbohydrate chain. Approximate molecular weight is 30,000 Daltons ⁶.



Synthesis, Action and Regulation of EPO secretion

The physiological path way of erythropoietin maintains tissue oxygenation by controlling the number of erythrocyte circulating in the blood.

Erythropoietin synthesized primarily in the peritubular fibroblast as a responsive mechanism of anemia or hypoxia, is a component of a complex feed back system that adjust the size of the red cell mass in response to the demand for oxygen by the tissue. After exposure to acute hypoxia determine the rapid accumulation in the kidney of specific erythropoietin messenger RNA (mRNA) which precedes the synthesis and secretion of the active hormone. The hormone first bind to cell surface receptor of BFU-E (Bust forming unite-Erethroid) cell. Which highly proliferate and require large amount of erythropoietin to progress into the next phase of development and it also prevent programmed cell death. Then BFU-E cells gradually ceases to multiply and enter into a critical erythropoietin dependent CFU-E (colony forming unite erythroid) stage.

Then CFU-E cells proliferate into erythroid precursor reticulocyte and finally into mature erythrocyte. Lastly in activation of the genes occur following oxygenation. This continue until it is signaled again by a hypoxic response mechanism, indicating that red cell mass has declined below normal level.⁷

Functions of erythropoietin ^{8,6}

1. Prevent apoptosis or programmed cell death among immature erythroid progenitors.

2. Stimulate erythropoiesis following hypoxia or anaemia and finally produce mature RBC and make adequate Hb concentration for tissue oxygenation.
3. It regulates RBC production.
4. It prevents anaemia of inflammation.

Causes of EPO deficiency in renal failure ^{9,10}

1. Destruction renal tissue mainly renal fibroblast.
2. Erythropoietin –producing fibroblast transformed into matrix producing fibroblast.
3. Absences of paracrine signal from closely adjacent tubular epithelium.
4. Local inhibition of Erythropoietin production by inflammatory cytokines.
5. No compensation of EPO production by liver.
6. Submaximul EPO response to an anaemic stimulus, reflecting inability of the disease kidney to produce adequate amount of EPO.

Indication of r-human erythropoietin therapy ^{9, 10,11}

- In case of end stage renal diseases (ESRD)
 - During maintenance haemodylasis
 - CAPD
 - Predialysis patients
 - Uremic children with haematocrite <30 or presences of anemic symptoms
- Anaemia in AIDS patients
- Anaemia associated with cancer chemotherapy which drugs causes' bone marrow depression.
- Development of anemia in premature and very low birth weight baby.
- In case of thalassemia
- Development of anemia in some chronic inflammatory diseases eg-tuberculosis, kala-azar, inflammatory bowl diseases etc.
- Development of anemia following major surgery .

Routes of administration of erythropoietin therapy in renal failure ^{13, 14,15}

Erythropoietin can be administered in following three routs-

- a. Subcutaneous
 - b. Intravenous
 - c. Intraperitoneal
- a. Subcutaneous- these rout is the most common method of administration for children with chronic renal

failure and for those receiving chronic peritoneal dialysis. It can be given once or twice per weeks. This method of administration leads to prolonged half life and decrease the total weekly doses. The total initial weekly dose have ranged between 30-300 units/kg. Where as maintenance doses vary between 60-600 units/kg/week.

- b. Intravenous- it generally reserved for children receiving chronic haemodialysis. This route is used through haemodialysis access site during dialysis. Its half life is short. Initial dose is 40-60 u/kg/ dialysis, and require 3 times a week. Children younger than five years of age frequently require higher weekly doses than older children and adults.(greater than 300u vs. 80-120u / kg.)
- c. Intraperitoneal administration was developed for peritoneal dialysis patients and was found to be most effective methods. The agent is given in small volume in dry peritoneal cavity. Where absorption could be maximized.

Principles of use of r-Human erythropoietin^{17,18, 19,20}

1. The response of r HUEPO is dose dependent and variable. Most patient will maintain a stable haematocrit of 32% and hemoglobin less than 11gm/dl with normal iron status. With 80-120u/kg/week subcutaneously in 2-3 divided doses or single doses.
2. Expected haemoglobin rise is 1-1.5 gm/dl/month.
3. Target haemoglobin is 11-12.5 gm /dl and target haematocrit is >33-37%. If target haemoglobin achieved continue same doses. If haemoglobin more than 12.5 gm /dl or rise of haemoglobin >2gm/dl/month then decrease dose of erythropoietin by 25%. If haemoglobin <11gm/dl increase dose by 25%.
4. Follow-up to monitor haemoglobin and haematocrit 2 weekly and iron status monthly. Optimum TSAT (Total percentage saturation of Transferrin) 20-50%. Optimum S.ferritin 100-800 ngm /ml.

Advantage of EPO therapy^{21,22,23,24}.

1. Correct anaemia of renal failure and other condition.
2. Improved number of abnormalities of platelets functions.
3. Relief of variety of Uremic signs and improves quality life parameters.
4. Reduce total cholesterol and triglyceride level.
5. Improved cerebral blood flow and cognitive function.

6. Improved haemodynamic and cardiovascular abnormalities.
7. It maintains target haematocrite 30%-36%.

Side effect of r-HIEPO^{17,24,25, 26}.

1. Hypertension (most common)
2. Headache (15% cases)
3. Thrombosis (due to haemolytic defect rises Hct. and platelets count)
4. Seizure
5. Influenza like syndrome (51%)
6. Reduce dialysis efficiency and increases dialyzer clotting
7. Resistance to EPO due to iron deficiency and rapidly increased erythropoiesis.

Conclusion

Anemia is an important complication of chronic renal failure. That is associated with poor quality of life, increased morbidity and mortality. Management of this clinical condition with iron therapy, blood transfusion and dialysis give only partial improvement. With the use of r-HUEPO give better improvement and good quality of life and hemoglobin concentration targeted at a predetermined level consistent with elimination of anemia related symptoms.

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