

EXPERIENCE OF ERYTHROPOIETIN IN ANEMIA OF END STAGE RENAL DISEASE

Pages with reference to book, From 310 To 312

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ABSTRACT

Recombinant human erythropoietin 50 units/kg intravenous twice a week was given to 9 anemic patients and end stage renal disease (ESRD) who were undergoing dialysis at the Kidney Centre. Of the total, 8 required no transfusion since the initiation of therapy and their haematocrit increased to approximately 29% or more with the improvement in general condition, sense of well being and exercise tolerance. One patient showed an increase in serum creatinine and two iron deficiency during therapy. In all cases blood pressure remained adequately controlled. No organ dysfunction or any other complication was observed (JPMA 41:310,1991).

INTRODUCTION

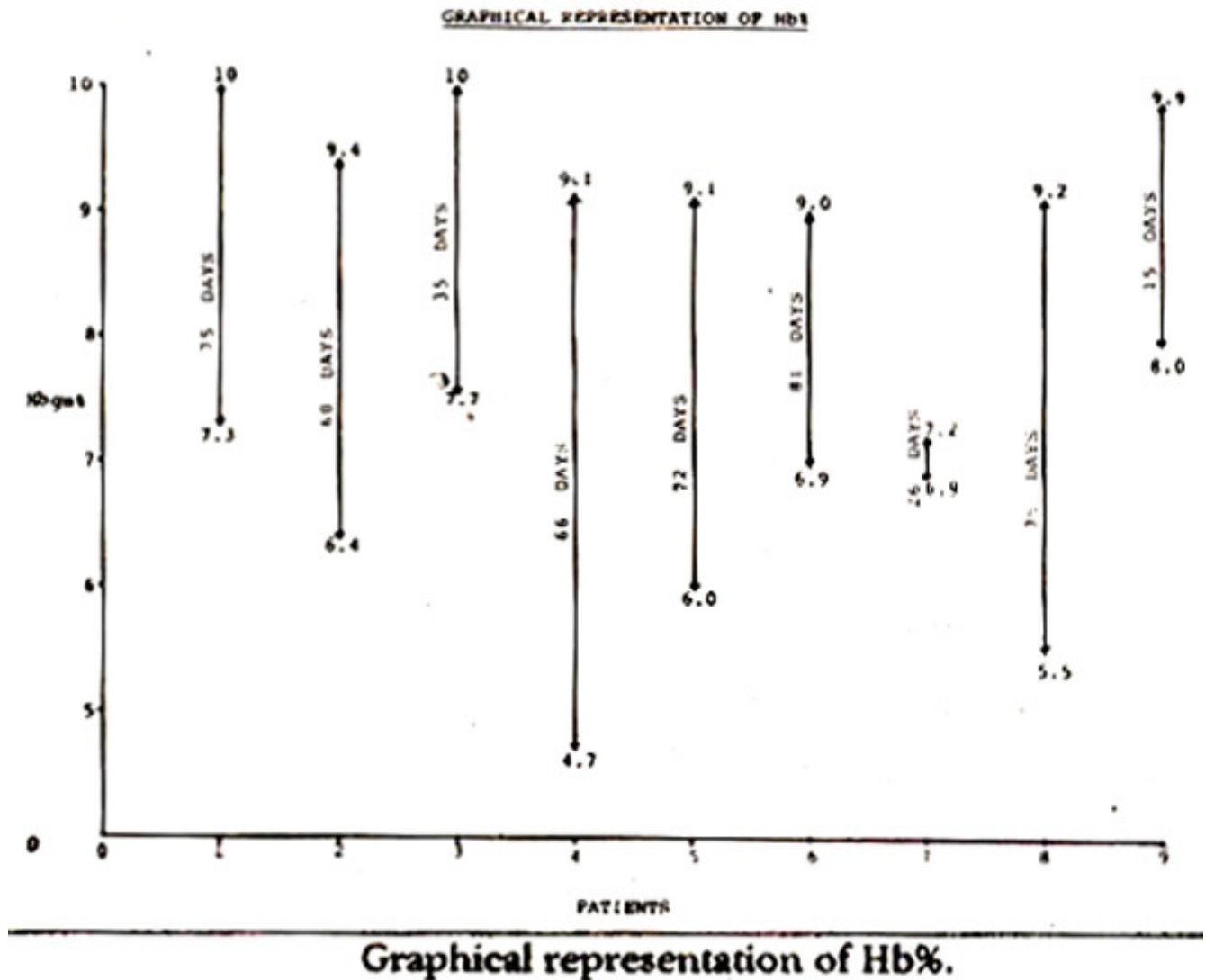
Anemia is a major and predictable complication of chronic renal failure. When ESRD evolves, anemia is usually severe and often impairs rehabilitation despite adequate dialysis therapy¹. The mechanisms underlying anemia are complex but mainly involve reduction of erythropoietin production and variable shortening of red cells survival¹⁻³. Iron deficiency, hypersplenism and aluminium induced microcytosis may aggravate the anemia of ESRD¹. Retained inhibitors and toxic metabolites in ESRD², impaired marrow function, osteitis fibrosa associated with hyperparathyroidism and folic acid deficiency all contribute to the development of anemia. Most of the patients are treated with blood transfusions but the response is temporary¹. Iron supplementation is required to prevent or correct iron deficiency^{3,4}. This study was conducted to evaluate the response of patient with anemia of ESRD to erythropoietin replacement therapy.

PATIENTS AND METHODS

Nine patients of ESRD diagnosed on ultrasound and creatinine clearance studies (less than 10 ml/min) referred from different hospitals and registered for maintenance haemodialysis at the Kidney Centre were included in the study. Informed consent was taken from all cases. Most patients were transfusion dependent. Of nine, 7 were hypertensive (adequately controlled) and 2 were normotensive. None had any history of seizures, sensitivity to mammalian derived product, albumin sensitivity or any associated systemic infection. Financial status of all cases justified the long term use of erythropoietin therapy. Serum iron, total iron binding capacity (TIBC), serum ferritin and transferrin saturation were evaluated before therapy and then every month (serum ferritin 100 ng/ml and transferrin saturation at least 20% prior to initiation of therapy). Haematocrit was assessed in the beginning and then weekly for at least 2-6 weeks. Total leukocyte and platelet count, urea, creatinine, electrolytes, inorganic phosphorus and potassium were monitored monthly. No cause other than uremia accounted for anemia. Erythropoietin was given in a dose of 50 units/kg body weight intravenously two times a week at the end of dialysis.

RESULTS

Nine patients (6 males, 3 females) were included in the study. Their ages ranged from 42 to 73 years with a mean weight of 54 kgs. Cause of ESRD was chronic nephritis in 4, chronic pyelonephritis in 2 and hypertension, polycystic kidney and diabetes mellitus in one each case. Blood group was B-positive in 5 and 0-positive in 4 cases. Duration on dialysis was between three months to one year. In 6 patients blood transfusion requirement was very often before the erythropoietin therapy. Since the initiation of therapy, 8 of 9 required no blood transfusion and only 1 required blood transfusion at very initial stages. In 7 hypertensives, blood pressure adequately controlled with anti-hypertensive therapy, no episode of rise in blood pressure was observed in 2 normotensives. At the initiation of therapy mean haemoglobin was 6.6 gm% and PCV 21.08%. Transferrin saturation was more than 20% and serum ferritin more than 100 ng/ml in 8, but less than 20% in 1. Total leukocyte and platelet count was within normal limits. Erythropoietin was started in all with a dose of 50 units/kg body weight (the minimum recommended dosage). Eight cases received twice weekly and 1 three times a week. Results of therapy on haemoglobin levels is shown in Figure.



No change in total leukocyte and platelet count was observed during therapy, urea, creatinine, electrolytes studies remained unaffected in 8 cases while a rise in serum creatinine was observed in 1 case. Oral haematinics were advised according to the individual's requirement. On an average 325 mg of ferrous sulphate and 3 mg of folic acid per day was given in divided doses. Patients were assessed clinically during therapy. General condition improved in all these patients.

TABLE. Present haematocrit and iron values.

Patient No.	Hb (gm%)	PCV (%)	Iron (Mgm%)	TIBC (Mgm%)	Ferritin (ng/ml)	Transferrin Saturation(%)	TLC (/cmm)	Platelet (/cmm)
1	9.1	28.2	53	284	46	19.0	5,100	144,000
2	9.4	29.0	70	260	300	26.0	4,700	180,000
3	9.0	29.0	80	336	281	23.0	4,100	207,000
4	9.1	30.3	51	276	69.8	18.5	4,200	225,000
5	9.5	31.2	64	229	100.0	24.0	4,900	150,000
6	9.0	29.0	119	318	342	37.0	6,800	270,000
7	7.0	22.2	120	288	347	41.3	5,300	225,000
8	9.4	30.2	106	194	420	56.0	7,200	223,000
9	9.9	30.9					5,600	250,000

Study is due on 27th May 1991

- Mean Hb 9.04 gm%

- Mean PCV 28.8%

Appetite improved in all but 1. Improvement in the sense of well being and exercise tolerance was observed in all. The reported complications of erythropoietin therapy such as hypertensive crises, myocardial infarction, cerebrovascular accident, transient ischaemic attacks, dialyzer clotting and blockage of vascular access was not observed in any patient. Neurological complications like seizures were also not observed.

DISCUSSION

Recombinant human erythropoietin have shown that it can fully correct anemia in patients undergoing haemodialysis. Renal origin of erythropoietin was demonstrated by Jacobson et al. They potentiated the search for humoral erythropoietic factor (erythropoietin). This hormone serves as one limb in the oxygen mediated feedback loop that controls the production of red cells and is produced in response to renal hypoxia. Recombinant human erythropoietin is a 165 amino acid glycoprotein manufactured by recombinant DNA technology. It has same biological effects as endogenous erythropoietin and is produced by mammalian cells into which recombinant erythropoietin gene has been introduced. Ninety percent of erythropoietin is produced by the kidney from peritubular capillary endothelial cells of renal cortex and outer medulla, less than ten percent is produced by the liver⁶. Half life of erythropoietin varies from 4-13 hours, detectable levels of EPO is maintained for atleast 24 hours. It is formulated as a sterile colourless, preservative free fluid for intravenous or subcutaneous administration. Each vial contains 2,000, 4,000, 10,000 units whose cost varies between Rs. 1,200 to over 3,000, therefore, the long time for which it has to be continued makes EPO beyond the reach of most of the patients. The age, duration of dialysis, blood group and weight of the patient had no effect on the response to erythropoietin. We started with the minimal recommended dosage of 50 units/kg body weight. The target response (Hb 9-10 gm%, PCV 28-30%) was achieved in less than three months in 8 patients and in 1 response is still awaited. This patient was re-evaluated but no cause other than uremia for anemia was found, so the dosage and the frequency of erythropoietin has been increased. The normotensives did not show any variation in blood pressure during therapy and in hypertensives no change in medication was required. Reduction in transferrin saturation, serum ferritin and plasma iron concentration were recorded in 2 patients during erythropoietin treatment, probably due to rapid increase in synthesis of haemoglobin. Iron supplementation is, therefore, required to prevent iron and ferritin depletion which might alter the response to erythropoietin^{7,8}. Seven transfusion dependent cases did not require any more transfusion after the initiation of therapy. This represents a major improvement as patients undergoing dialysis have no longer the risk of iron

overload, exposure to infection or development of cytotoxic antibodies. The correction of anemia as expected was accompanied with substantial improvement in patients rehabilitation and the quality of life and this was maintained throughout the period of study. In only 1, rise in serum creatinine was observed during the therapy, but it was not significant enough to require any change in the frequency of dialysis. In the same patient the initial improvement in the appetite later decreased probably due to hypophosphatemia (serum phosphorus was 1.5-2.0 mg). In2roduction of dairy products in his diet improved not only his serum phosphorus level (3.0 mg) but also the appetite. During the 8 months period of this study, none of the reported complications to erythropoietin therapy were observed in any of the patients. The human erythropoietin therapy can therefore be safely recommended as the treatment of choice in the anemia of patients with ESRD who can afford the drug.

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