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Treatment of Renal Anemia with Recombinant Human Erythropoietin

Aizaz Mand Ahmad, Tahir Shafi, Tashbeeb Gulzar
Department of Nephrology, Shaikh Zayed Postgraduate Medical Institute, Lahore.

SUMMARY

Anemia in chronic renal failure is a world wide problem and often its treatment is unsatisfactory. Availability of recombinant human erythropoietin (rHuEpo) has revolutionised the treatment of anemia of chronic renal failure. We treated 30 patients with established renal failure and anemia with human erythropoietin using a dose of 30 IU/kg body weight subcutaneously, twice a week. Males were 17 (56.7%) and females were 13 (43.3%). Mean age was 53.41±15.38 years. Etiological diagnosis was hypertension in 12 (40%) diabetic nephropathy in 8 (26.6%) chronic pyelonephritis in 2 (6.7%) chronic glomerulonephritis in 3 (10%) amyloidosis in 1 (3.3%) while 4 patients (13.3%) had chronic renal failure of uncertain etiology. Out of these, 25 patients were in end stage renal failure and on thrice a week hemodialysis, remaining 5 were on conservative treatment. Duration of dialysis was 3 months to 2.5 years. Base line pre-treatment mean hemoglobin was 7.21±0.89 g/dl. Mid week mean blood urea was 141±51.72 mg/dl and mid.week mean serum creatinine was 10.95±4.1 mg/dl. After treatment with rHuEpo statistically significant improvement was noted in hemoglobin level which progressively rose from 7.21 g/dl to 8.7 g/dl at one month (P=0.059) to 9.2 g/dl at two months (P=0.03) and to 9.7 g/dl at three months (P=0.06) approaching significant value. No significant change was observed in serum potassium, phosphorous or albumin levels but slight rise in blood pressure needed dose adjustments. We conclude that in small doses recombinant human erythropoietin given subcutaneously is quite safe, relatively free from side effects and an effective agent in treatment of anemia of chronic renal failure.

INTRODUCTION

The association of anemia with chronic renal failure was first described by Richard Bright more than 150 years ago. Anemia in chronic renal failure has added clinical significance than was previously recognised. Almost all the patients with chronic renal failure throughout the world are anaemic and more than 50% of these are symptomatic of anemia. In a study by Gutman et al.[1] out of 100,000 patients suffering from end stage kidney disease undergoing regular hemodialysis in the United States only 3% had a normal hematocrit. Despite regular dialysis only 33% patients were rehabilitated, the rest continued to remain symptomatic of fatigue, weakness and poor exercise tolerance mainly induced by anemia[2]. As the severity of anemia usually though not always directly relates to the severity of renal failure, it was thought that anemia is due to effects of uremia[3]. Since then various investigators have been trying to explain the etiology and pathogenesis of anemia in chronic renal failure.

It is an established fact now that anemia of chronic renal failure is invariably normochromic and normocytic in nature and is associated with a hypoproliferative bone marrow provided other factors like nutritional deficiencies, blood loss, and hemolysis are not present[4].

The pathophysiology of anemia of chronic renal failure is multifactorial. The major mechanisms that have been recognised to contribute towards anemia in chronic renal failure are:-

1. Shortened red cells survival.
2. Uraemic toxins and retained inhibitors of

erythropoiesis.
3. Iron and folate deficiency.
4. Bleeding tendency.
5. Osteitis fibrosa cystica with hyperparathyroidism.
6. Erythropoietin deficiency.

The last factor erythropoietin deficiency has now been considered to be of immense importance. Because kidneys are the primary site of erythropoietin production and in diseased kidneys its production is markedly diminished.

The treatment of anemia of chronic renal failure has also been quite unsatisfactory. Institution of chronic dialysis can improve anemia of chronic renal failure, but repeated blood transfusions have been the mainstay of treating anemia in dialysis patients. Blood transfusions correct the anemia but are associated with the problems of transmission of viral infections, transfusion reactions and iron overload.

Androgenic steroids have been tried with mild or variable response.

Eschback et al. demonstrated correction of anemia in chronically uremic sheep by daily injections of erythropoietin rich plasma and ever since the availability of genetically engineered recombinant human erythropoietin (r-HUEPO) commercially in June, 1989 a tremendous breakthrough has occurred in the management of anemia of chronic renal failure in both predialysis and dialysis patients[5]. Several large multicentre trials are on their way to establish the efficacy, optional dosage, route, safety and adverse effects of erythropoietin in anaemic patients with chronic renal failure, but to date only few published studies from our country are available on the use of erythropoietin in anemia of chronic renal failure.

AIMS AND OBJECTS

Purpose of the study was to see the efficacy and safety of recombinant human erythropoietin in the treatment of anemia of chronic renal failure.

PATIENTS AND METHODS

The study was conducted on 30 patients from both sexes, who were diagnosed to have chronic renal failure and were suffering from anemia of significant severity. Human recombinant erythropoietin was used in a dose of 30 units/kg body weight subcutaneously twice a week for a period of 3 months.

Inclusion criteria

Only those patients fulfilling following set out criteria were enrolled in the study:

1. Informed consent from the patient.
2. Established diagnosis of chronic renal failure in patients on hemodialysis or conservative treatment.
3. Hemoglobin $\leq$ 8.0 g/dl.
4. Supervised drug administration.

Exclusion criteria

Patients with following pathological states were excluded from the study.

1. Uncontrolled hypertension.
2. Iron deficiency state.
3. Severe secondary hyperparathyroidism.
4. Patients diagnosed to have sepsis.
5. Clinically evident aluminium toxicity.
6. B12 and folate deficiency.
7. Anemia of cause other than chronic renal failure.
8. Patients getting blood transfusion during study period.

Patient evaluation procedure

1. **Detailed Medical History**
With special emphasis on existence of systemic disease like diabetes, hypertension, intake of drugs. A thorough account of all the symptoms was made to ascertain presence of other illnesses.

2. **History of Anemia**
Fatique, angina, dyspnoea, work performance, was assessed to know the severity of anemia. Any reversible factor like blood loss, hemolysis intake of food, malabsorption etc. were taken into account. Number of blood transfusions and dependency on these was noted.

3. **History of Renal Disease**
Duration, severity, etiology and existence of renal disease in the family was noted. All complications of chronic renal failure were looked for and noted.

4. Physical Examination

A thorough physical examination was done especially to look for purpura, echymosis, pallor, blood pressure, pulse rate, body temperature or any focus of infection were and findings recorded in the proforma. Any change during the study period was noted on each visit.

5. Laboratory Data

Base line laboratory hematological data and biochemistries were recorded at the start of the study and at 2 weeks interval for a period of 3 months. Iron stores were assessed where it was possible to do so.

Drug administration and dosage

Human recombinant erythropoietin injection in a dose of 30 IU/kg body weight was given subcutaneously under supervision twice weekly using an insulin syringe.

Patient on hemodialysis received the dose at the end of dialysis session. Goal of erythropoietin therapy was to achieve a haemoglobin around 9.5-10 g/dl. When insufficient or no response was achieved after 4 weeks of treatment, the dose was increased to 50 IU/kg body weight. Routine concomitant medication for the treatment of chronic renal failure was allowed. Iron and folic acid supplements were given to all patients included in the study. A fortnightly record of their visits was kept.

Their symptoms, physical findings, new symptoms or adverse effects were noted. Laboratory data on each visit was also recorded accordingly.

RESULTS AND OBSERVATIONS

A total of 30 cases diagnosed to be suffering from chronic renal failure were included in the study. Profile of these patients is given in Tables 1 and 2. Males were 17 (56.7%) and females 13 (43.3%). Mean age was 53.41±15.38 years. Etiological diagnosis was hypertension in 12 (40%), diabetic nephropathy, in 8 (26.6%) chronic pyelonephritis 2 (6.7%), chronic glomerulonephritis in 3 (10%), amyloidosis in 1 (3.3%) while 4 patients (13.3%) had chronic renal failure of uncertain etiology. End stage renal failure was present in 25 patients who were on three times weekly hemodialysis, remaining 5 patients were on conservative treatment. Duration of dialysis was 3 months to 2½ years. Three patients were blood transfusion dependent and needed at least one unit of blood every month.

Table 1: Age and sex distribution of the patients.

	Number	*Percent*
Age group (Years)		
10-19	3	10
20-29	-	-
30-39	3	10
42-49	2	6.7
50-59	9	30
60-69	10	33.3
70-79	3	10
Sex		
Male	17	56.7
Female	13	43.3
Total	**30**	**100.0**

Table 2: Etiological diagnosis.

Diagnosis	*Number*	*Percent*
Amyloidosis	1	3.3
Chronic GN	3	10
Ch. Pyelonephritis	2	6.7
Unknown etiology	4	13.3
Diabetic nephropathy	8	26.6
Hypertenive Nephropathy	12	40
Total	**30**	**100.00**

Pretreatment symptoms attributed to anemia were weakness, fatigue, lethargy and malaise and were reported by nearly 100% patients. Two elderly patients one male, and one female experienced angina pectoris during hemodialysis sessions and 4 patients complained of shortness of breath on slight exertion. Mean pre-treatment weight was 62.66 kg. No patient was lost to follow up.

Base line pretreatment laboratory parameters showed a mean haemoglobin concentration of 7.21±0.89 g/dl. Mean blood urea was 141±51.72 mg/dl, mean serum creatinine was 10.95±4.1 mg/dl, mean serum potassium was 5.13±0.63 mmol/l, mean serum phosphorous was 6.47±2.38 mg/dl and mean serum albumin was 4.01±0.63 g/dl, serum ferritin

levels were done where it was possible to do so. One patient had serum ferritin of 1310 ng/ml. One patient developed iron deficiency while on erythropoietin therapy and was therefore given parenteral iron therapy.

After treatment with recombinant human erythropoietin in a dose of 30 units/kg twice weekly subcutaneously, significant improvement was noted in symptoms of the patients. Angina reported in 2 patients disappeared and the blood transfusion dependency was eliminated in all the 3 patients. Symptoms pertaining mainly to anemia although persisted in one third of cases, the subjective severity markedly decreased and they felt much better.

Statistically significant improvement was noted in haemoglobin level which progressively rose from 7.21 to 8.7 g/dl after one month (P=0.059) to 9.2 g/dl at the end of second month (P=0.03) to 9.7 g/dl at the end of the study period (P=0.06) (Fig. 1).

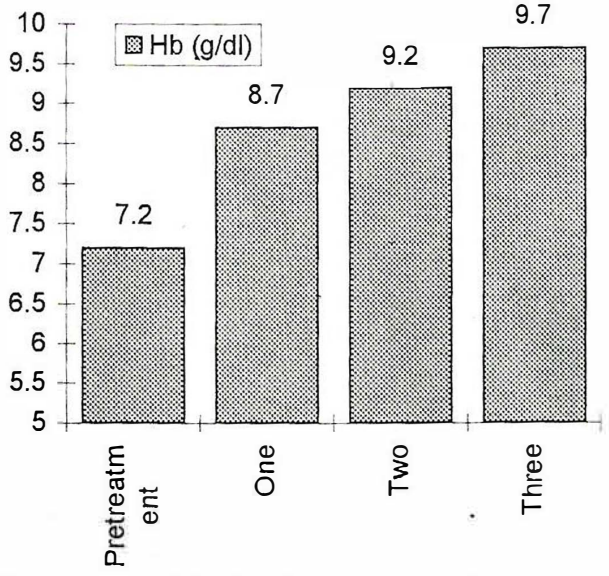

Fig. 1: Hemoglobin levels with rHuEPO therapy.

Mean post treatment blood urea values were somewhat higher than pretreatment figure and showed a progressive rise over 3 months (141 mg/dl to 154 mg/dl). No significant changes were observed in the serum potassium, phosphorous or albumin levels (Table 3).

At the end of study period there was an increase of 1.1 kg in mean dry weight. This could be due to better eating habits and sense of well being achieved after correction of anemia. In 3 patients who were hypertensive, an increase in antihypertensive dose was needed to control the blood pressure. One patient at the age of 82 years complained of nocturnal penile tumescence. Apart from slight pain at the injection site no other complaints or side effects were recorded.

DISCUSSION

The discovery by Jacobson et al. in 1957 that kidney was the organ responsible for 80-85% of the erythropoietin production in the body explained why anemia is an inevitable accompaniment of chronic renal failure. The research in this direction progressed very fast over next years. The gene was cloned and found to be located on long arm of chromosome 7 in 1983 by Lin et al. and Jacobs et al. In next couple of years erythropoietin was produced by recombinant technology and clinical trials were started in 1985-1986. Huge amount of literature has been published on various aspects of erythropoietin use. In these trials the drug has been found to be effective in almost all cases and was remarkably free of serious side effects.

In initial clinical trials erythropoietin was used in a dose of 100-150 units/kg and intravenously but over the last 2-3 years there has been a trend to use smaller doses of erythropoietin subcutaneously.

In countries like ours till about 2 decades ago, majority of chronic renal failure patients used to die but with the start of hemodialysis units they saw the dawn of a new era of management. While dialysis took over the excretory function of the kidney, its endocrine function could not be replaced and anemia was treated with blood transfusions. Sensitization rate, introduction of transmissible infections like hepatitis and AIDS with poor control on screening service at blood banks, blood transfusions were a major threat to life.

From Pakistan probably the first clinical trial[6] on 9 patients with chronic renal failure and anemia on hemodialysis using low dose of erythropoietin (50 u/kg intravenously). The drug was found to be very effective and virtually free of side effects. In developing countries like ours, cost is a major limiting factor of its wide spread use. The purpose of this clinical trial was to see if a still smaller dose of 30 u/kg given subcutaneously was effective and cost effective. Since half life of subcutaneous injection is longer than intravenous, we preferred to use subcutaneous dose.

Table 3: Biochemical parameters before and after erythropoietin therapy.

Duration	*B. Urea mg/dl*	*S. Creat mg/dl*	*S.K^+ mmol/l*	*S.PO_4^- mg/dl*	*S. Alb. g/dl*	*S.Ca^{++} mg/dl*
Pretreatment	141.1	10.95	5.13	6.47	4.01	7.91
1 Month	141.5	11.099	5.27	6.67	4.03	7.74
2 Months	154.1	12.50	5.14	6.73	4.16	7.63
3 Months	157.8	12.96	5.22	6.79	4.53	7.5

The results of this study are quite encouraging showing marked subjective improvement in grades of symptoms attributable to anemia. Total elimination of blood transfusion dependency and increase in dry weight are big successes. Hemoglobin level improved considerably from initial pre treatment values of 7.21 g/dl to 8.7, 9.2 and 9.7 g/dl after 1, 2 and 3 months of recombinant human erythropoietin therapy respectively. These values were statistically found to be significant. The maximum rise in haemoglobin level was seen (1.5 g/dl) during the first 4 weeks of treatment, thereafter the progressive rise continued to occur but probably for the reasons that a very small dose of erythropoietin was used and the desired effects were seen, dose was not increased. We observed a rise in blood pressure above baseline pretreatment readings in 3 patients which was easily managed by increase in antihypertensive therapy. Serum potassium remained normal, there was a slight upward trend in phosphorous levels but is not significant. A significant rise in mean urea and creatinine values occurred in our patients and these have previously been noted by other observers[7]. Increase in hematocrit leads to better overall health scores and better eating habits on one hand and decreased clearance of solutes and their dialysability on the others. Minor adjustments in the dialysis prescription are needed to cover for these discrepancies. Financial constrains are a major cause of suboptimal dialysis and drug therapy. Majority of patients in this study are not adequately dialysed and this may be one of the reasons of high urea and creatinine values, since no modification were done in the dialysis prescription. Moreover, deteriorating residual renal function may be another cause of rise in urea and creatinine.

Some side effects described with erythropoietin therapy are due to increase in hematocrit, like hypertension and vascular access closure. As mentioned, earlier although 3 of our patients had hypertension, none had problems of vascular access closure. No adjustments in the heparin requirements had to be done. Less number of complication in our patient could be due to gradual and not too high levels of haemoglobin achieved during the trial.

The most commonly mentioned side effect of erythropoietin therapy is the development of iron deficiency anemia due to greater need of iron for red blood cell production[8]. Adequate iron stores are ensured before therapy is started. One of our patients had very high serum ferritin levels due to previous history of repeated blood transfusions on top of prescribed iron supplements. Treatment with recombinant erythropoietin resulted in gradual reduction in serum ferritin levels. One patients who was not responding adequately was found to have developed iron deficiency and was given parenteral treatment with iron. No patient had fits and one elderly male patient complained of frequent troublesome nocturnal penile tumescence. Allergic reactions to drug were not seen in any of our patients. Disappearance of angina after correction of anemia was an added benefit in 2 patients. The dose of 30 u/kg twice weekly was just sufficient to keep the haemoglobin within a reasonable range without any significant side effects and justifies such a policy when the cost of the drug is high.

CONCLUSION

It can be concluded from the results of the present study that availability of recombinant human erythropoietin has revolutionised the treatment of anemia of chronic renal failure, it has eliminated the dependency on blood transfusions and their hazards. The drug is effective in correcting

anemia of chronic renal failure of all grades in low doses. It is relatively free of side effects and judicious use with gradual rise in haemoglobin values does not cause serious complications. Further studies are needed to confirm its efficacy in low doses.

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The Authors:

Aizaz Mand Ahmad
Senior Registrar,
Department of Nephrology,
Shaikh Zayed Postgraduate Medical Institute,
Lahore.

Tahir Shafi
Professor of Nephrology
Head Division of Medicine
Shaikh Zayed Postgraduate Medical Institute,
Lahore.

Tashbeeb Gulzar
Senior Registrar,
Department of Nephrology,
Shaikh Zayed Postgraduate Medical Institute,

Lahore.

Address for Correspondence:

Aizaz Mand Ahmad
Senior Registrar,
Department of Nephrology,
Shaikh Zayed Postgraduate Medical Institute,
Lahore.