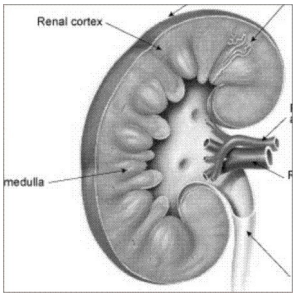
ORIGINAL PROF-864

CHRONIC RENAL FAILURE;
TREATMENT OF ANEMIA WITH ERYTHROPOIETIN AND IRON



DR. OSMAN ALI JAN, MBBS, FCPS
Department of Medicine
PAC Hospital Kamra

Dr. TALAT BASHIR, MBBS
Combined Military Hospital, Multan

ABSTRACT ... Oajan_2002@yahoo.com. talatbashir22@hotmail.com **Objectives:** This study on anemia in chronic renal failure patients was aimed at evaluation and comparison of response to erythropoietin therapy in iron deficient groups treated with parenteral vs iron deficient group treated with oral iron ; keeping iron replete patients as controls. **Study design:** Study design was case control study. **Place and duration of study:** The study was carried out at department of medicine Military hospital Rawalpidi and Armed forces institute of Urology; from 1997-1998. **Subject/Methods:** A total of 59 patients were recruited. Comparison of the change in hemoglobin, hematocrit, and reticulocyte count and serum ferritin levels was made. They were divided into three groups based on their serum ferritin levels. Group I (n=18) and group II (n=16) consisted of iron deficient patients. Group III (n=25) consisted of iron-loaded individuals and they were treated with erythropoietin alone. This group acted as the control group for the study. **Results:** The hematocrit increased by an average of 6% in group I, 2% in group II and 5% in group III. The serum ferritin levels increased by an average of 147.51 µg/l in group I. Group II on oral iron showed an increment of only 77.1 mg/l. Group III that consisted of iron loaded patients showed a decrease of 594.2 mg/l in serum ferritin levels while on erythropoietin. **Conclusions:** (i) It was concluded that erythropoietin improved anemia in patients with chronic renal failure, parenteral iron having a definitive advantage over oral iron therapy. This response is augmented by supplementing iron in iron deficient patients. (ii) Conversely, functional iron deficiency, i.e. the inability to utilize iron in iron replete patients for erythropoiesis exhibit improvement with erythropoietin therapy.

Key Words: Anemia, Chronic renal failure, Erythropoietin, ferritin, Iron therapy

INTRODUCTION

Anemia is the most common and treatable complication of chronic renal failure. If corrected adequately, it significantly improves the quality of life of patients. Our study aimed at evaluating and comparing the response to erythropoietin therapy in anemic patients by treating iron deficient patients with parenteral and oral iron and keeping iron replete patients as controls.

A comparison of the change in hemoglobin, hematocrit, and reticulocyte count and serum ferritin levels was made on a total of 59 patients treated with erythropoietin and iron. They were divided into three groups based on their serum ferritin levels. Group I (n=18) and group II (n=16) consisted of iron deficient patients. They were placed on erythropoietin with parenteral and oral iron respectively. Group III (n=25) consisted of iron-loaded

individuals and they were treated with erythropoietin alone. This group acted as the control group for the study.

The results showed a mean increase in hemoglobin of 1.49 g/dl, 0.80 gm/dl and 0.98 gm/dl in groups I, II and III respectively. The hematocrit increased by an average of 6% in group I, 2% in group II and 5% in group III. The serum ferritin levels increased by an average of 147.51 mg/l in group I. Group II on oral iron showed an increment of only 77.1 mg/l. Group III that consisted of iron loaded patients showed a decrease of 594.2 mg/l in serum ferritin levels while on erythropoietin. The reticulocyte count showed an increment of 2.77%, 1.48% and 2.56% in groups I, II and III respectively.

CONCLUSION

It was concluded that erythropoietin improved anemia in patients with chronic renal failure. This response is augmented by supplementing iron in patients who are iron deficient. Among the modes of iron supplementation, parenteral iron has a definitive advantage over oral iron therapy.

MATERIALS AND METHOD

Patient Population

This comprised of a total 59 randomly selected patients of chronic renal failure between ages 20–40 years. They were divided into three groups. These groups were created based on the treatment designed as follows:

Group I Erythropoietin and parenteral iron.
Group II Erythropoietin with oral iron.
Group III Erythropoietin alone.

Inclusion Criteria:

Patients were selected for the study on the basis of the following:

- Presence of end stage renal disease (ESRD) and chronic renal failure.
- Anemia with hemoglobin levels below 8.0 g/dl.
- Creatinine clearance below 15 ml/min measured on 24-hour urine samples.

Exclusion Criteria:

Patients were physically examined in detail and underwent blood counts, urinalysis, stool for occult blood, liver function tests, chest X-rays and blood glucose levels. The following conditions were ruled out prior to induction;

- A history of hypertension, seizures or thrombotic episodes in the past.
- An acute infectious process.
- Evidence of blood losses from the gastrointestinal tract.
- Excessive or abnormal vaginal blood losses in case of females.
- Concomitant liver disease.
- Pulmonary tuberculosis – as it could cause anemia of chronic disease and impair responses to erythropoietin therapy.
- Diabetes mellitus.

Basis of Grouping Patients:

The placement of patients into groups was based on their serum ferritin levels performed at the start of the study. They were assessed weekly for clinical improvement and laboratory tests were performed to evaluate their response to treatment.

Individuals found to have serum ferritin levels less than 100 mg/L were considered iron deficient and were randomly assigned to group I and II. Patients found to have serum ferritin levels more than 500 µg/L were considered to be iron replete and placed in the control group III.

Methodology:

Each patient was studied for a minimum period of 8 weeks. All patients were started on erythropoietin at a dose of 25 IU/kg body weight three times per week in subcutaneously administered doses.

Intravenous iron was started in Group I patients after calculating individual iron requirements based on the

following formula;

Total iron deficiency (mg) = Hb iron deficiency-depot iron Hb iron deficiency (mg) = Body weight (kg) x (normal Hb – actual Hb g/dl) x 0.24

A bolus dose of 500 mg IV was given to cater for depot iron and the rest of the requirement was given IV on alternate days till the completion of calculated iron deficiency. Oral iron was given to Group II in the form ferrous fumarate tablets consisting of 115 mg elemental iron daily. This was supplemented with 100 mg ascorbic acid per day.

All patients were monitored weekly with hemoglobin and reticulocyte counts. Hematocrit values were performed every 2 weeks and serum ferritin values were assessed every 4 weeks. Urea, creatinine, sodium and potassium levels were evaluated both before and after hemodialysis sessions.

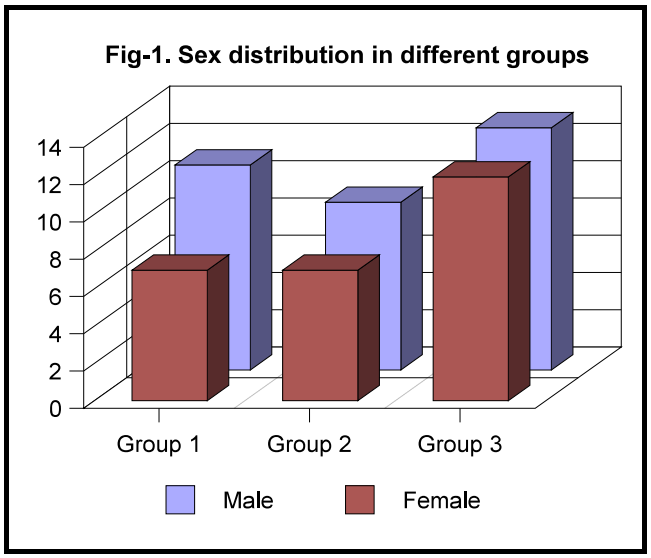
RESULTS

Our study consisted of 33 (55.9%) males and 26 (44.1%) females. Out of these 69.5% (n=41) underwent alternate and 30.5% (n=18) were on twice weekly, 4 hourly hemodialysis sessions.

At start of the study group I had a mean hemoglobin level of 6.81±0.97, mean hematocrit of 21±1.5 and serum ferritin levels at 75.83 ±16.51 µg/L.

In group II, the mean hemoglobin was 7.01 ± 1.06, mean hematocrit was 24.±2.1 and serum ferritin levels were 72.94±12.81 µg/L.

In group III, the mean hemoglobin level was 6.93±1.02, mean hematocrit was 23±1.02 and serum ferritin levels were 1107±228.95 µg/L.



During the course of the study, all parameters were compared at the start and then in the 4th and 8th week.

A comparison of baseline parameters in the three groups is given in Table 1 and the sex distribution in the groups is shown in Figure 1

Table I: Base line Parameters of Patients Enrolled

Parameters	Group I (n=18)	Group II (n=16)	Group III (n=25)
Male	11 (61.11%)	9 (56.25%)	13 (52%)
Female	7 (38.88%)	7 (43.75%)	12 (48%)
Mean Hemoglobin(g/dl)	6.81±0.97	7.01±1.06	6.93±1.02
Mean Hematocrit(%)	21±1.5	24.±2.1	23±1.02
Serum Ferritin Levels (µg/L)	75.83±16.51	72.94±12.81	1107.08±228.95

In Group I there was an increase of 1.49±0.99 g/dl in the hemoglobin concentration, a 21.88% rise in hemoglobin compared to the base line value. Hematocrit levels increased by 6±1.47%, a 28.57% increase from the baseline. Serum ferritin showed an average increase of 147.51±mg/L. The reticulocyte count rose by 2.77±0.41%.

Group II showed an average increase of 0.80±1.05 g/dl in the hemoglobin levels, an 11.41% rise from the base line value. There was an increase of 2±1.47% in the hematocrit levels, an 8.33% increase from the baseline. Serum ferritin showed an average increase of only 77.1 µg/L and the reticulocyte count rose by 1.48±0.47%.

Group III showed a rise of 0.98±0.98 g/dl in the hemoglobin levels, a 14.14% rise in from the base line value. The hematocrit increased by 5±1.31%, a 21.74% rise from the baseline value. Serum ferritin decreased by an average value of 594.2 µg/L and the reticulocyte count improved by 2.56±0.36%.

A percentage increase in hemoglobin and hematocrit at the end of 8 weeks was calculated for the three groups as mentioned in table 6 and 7 respectively.

The detail and graphic representation of the study results is presented in the following pages as per Tables 6 to 9 and Figures 3 to 6.

Table II: Comparison of Hemoglobin Levels (g/dl) At Different Stages of Study

% Increase in hemoglobin	Group I	Group II	Group III
Week 1	6.81±0.97	7.01±1.06	6.93±1.02
Week 4	7.59±1.04	7.4±1.05	7.36±0.99
Week 8	8.3±0.98	7.81±1.04	7.91±0.95
After 8 Week	21.88%	11.41%	14.14%
(P Value> 0.05)			

Table III: Change in the hematocrit values in response to erythropoietin

% Increase in hematocrit	Group I	Group II	Group III
Week 1	21±1.5	24±2.1	23±1.02
Week 4	23±1.32	25±0.58	25±1.08
Week 8	27±1.6	26±1.08	28±1.83
After 8 Week	28.57%	8.33%	21.74%
(P Value> 0.05)			

To estimate the significance of results, p values were calculated using the one tail t test. Both groups I and II were compared with the control (group III) and these values were found to be consistently > 0.50.

Table IV: Changes in mean ferritin levels with erythropoietin

	Group I	Group II	Group III
Week 1	75.83	72.94	1107.08
Week 4	126.66	96.57	864.61
Week 8	223.34	150.04	512.88

Fig-5. Reticulocyte response to erythropoietin

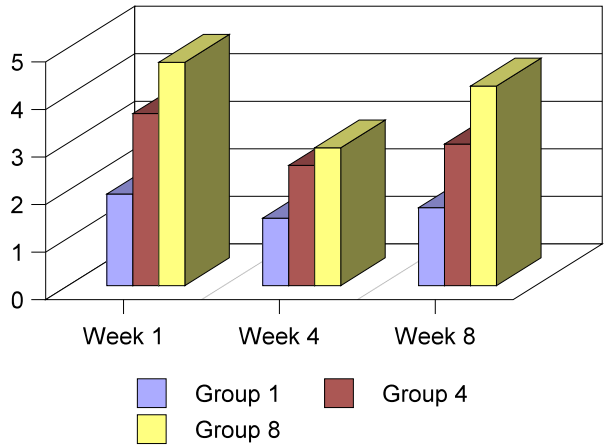


Table V: Reticulocyte count response to erythropoietin			
	Group I	Group II	Group III
Week 1	1.93±0.37	1.42±0.66	1.64±0.73
Week 4	3.62±0.48	2.53±0.35	2.98±0.19
Week 8	4.7±0.39	2.9±0.41	4.2±0.16

Anova test was applied to evaluate the variance within each group and between the individual groups. The variance in group I, II and III was 0.826, 1.077 and 0.915 respectively. The calculated p value was > 0.05 (p=0.38).

DISCUSSION

This study was conducted to evaluate the effects of erythropoietin treatment of anemia of chronic renal failure. It further endeavored to assess the difference of effect of oral iron versus parenteral supplementation on response to erythropoietin in iron-depleted individuals. A control group consisting of iron-loaded patients was included who were given erythropoietin alone.

Our study design initially aimed at increasing the hemoglobin levels by 2 g/dl, irrespective of the time taken to achieve this end, but it was curtailed to 8 weeks due to financial restraints.

We aimed at a rise in hemoglobin of approximately 1 g/dl per month. As documented in literature, the rise in hemoglobin does not start before 2 weeks of erythropoietin therapy, provided there is no iron deficiency. This response, in some cases, may take as long as 6 to 10 weeks.

All parameters monitored during the study showed a variable but favorable response to erythropoietin therapy. The most significant improvement in hemoglobin (a mean increase of 1.49 g/dl), hematocrit (a mean increase of 6%) and reticulocyte count (mean increase of 2.77%) was seen in patients treated with erythropoietin and IV iron (Group I).

Hemoglobin measured in other groups showed an increase of 0.8 g/dl increase in patients on oral iron and a 0.98 g/dl increase in the control group.

The hematocrit increase in groups II and III was 2% and 5% respectively. The reticulocyte count in groups II and III were of the order of 1.48% and 2.56% respectively.

The serum ferritin level increase in group II. showed an increment of only 77.1 mg/l. Group III, on the other hand, that consisted of iron loaded patients, showed a decrease of 594.2 mg/l in the ferritin levels following erythropoietin therapy.

Analysis with Anova demonstrated that the results were not statistically significant (p=0.38). The reasons for such large values could be explained as follows:

The duration of this study was 8 weeks whereas similar studies have been conducted over an average period of 6 months[1].

A longer period of investigation might improve the prospects of achieving meaningful results vis a vis the role of iron and erythropoietin in treating chronic renal failure.

The hemoglobin levels achieved were lower as compared to other studies on the subject. The possible reasons for this are as follows:

The dose of erythropoietin used was lower than that used in comparable studies. The doses used in other studies have ranged from 75 IU/kg body weight in the initiation period to 150 IU/kg body weight.

We used acetate hemodialysis in our study which has shown to have a significant suppressive effect on plasma erythropoietin levels in anemic chronic renal failure patients[1].

Finding a convenient and economical dosing schedule for erythropoietin therapy has resulted in studies with conflicting results. Schaller et al[1] showed that using the subcutaneous route, the dose of erythropoietin required

to maintain a target hematocrit was reduced by an average of 30% this view is supported by Kaufman et al[1]. On the contrary De-Schoenmakere et al[1] concluded that conversion to subcutaneous route did not lower to requirement for erythropoietin.

There is no significant difference in the bioavailability of subcutaneous erythropoietin depending on the site of administration as investigated by Jensen-JD et al[1] comparing the injecting of erythropoietin in to the thigh and the abdominal wall. However, the estimated half life of absorption was significantly longer after injection in the thigh than after abdominal application. In our study we used the forearm skin for injection.

Hussain R et al have evaluated once weekly administration of erythropoietin in the dose of 50 IU/kg body weight[1]. Their study showed a success rate of 84% with hemoglobin increase from 7.5 g/dl to 9.5 g/dl. On the other hand, Cheung et al[1] showed that the pharmacologic response to erythropoietin alfa is a function of dose and dosing regimen. Repeated administration of erythropoietin alfa was more effective in stimulating a reticulocyte response than single-dose administration of the same total amount of erythropoietin alfa.

Assessment of body iron stores is important for gaining maximum benefit from erythropoietin therapy. Initially it was suggested that body iron stores should be measured by an array of assays. Morris et al[1] have challenged this view. In their study on nine children with chronic renal failure they found serum ferritin to be the best predictor of iron deficiency. Another study reported that serum ferritin was being used by 98% of the nephrologists for assessment of iron status and 48% considered it the single most important parameter[1].

Oral iron therapy has a limited role to play in the correction of iron deficiency in chronic renal failure. Markowitz et al[1] have concluded that oral iron fails to maintain iron stores in iron replete patients.

Routine screening for other causes of anemia in patients with chronic renal failure like folate deficiency, B_{12} deficiency, hyperparathyroidism or aluminum toxicity have not been found to be cost effective and it is suggested that anemia screening should be limited to tests identifying iron deficiency[1].

CONCLUSIONS

It was concluded that erythropoietin improved anemia in patients with chronic renal failure. This response is augmented by supplementing iron in patients who are iron deficient. Among the modes of iron supplementation, parenteral iron has a definitive advantage over oral iron therapy.

The most efficient method for iron delivery is intravenous iron and helps to rapidly build iron stores in patients with low serum ferritin levels.

Conversely, iron loaded patients who demonstrate functional iron deficiency, i.e. the inability to utilize iron for erythropoies is benefit from erythropoietin therapy by increasing the hemoglobin and reducing iron stores.

REFERENCES

1. Markowitz-GS; Kahn-GA; Feingold-RE; Coco-M; Lynn-RI: **An evaluation of the effectiveness of oral iron therapy in hemodialysis patients receiving recombinant human erythropoietin.** Clin-Nephrol. 1997 Jul; 48(1): 34-40

2. Wiecek-A; Franek-E; Kokot-F; Rudka-R: **Influence of acetate and bicarbonate hemodialysis on the plasma erythropoietin concentration in patients with chronic renal failure.** Int-J-Artif-Organs. 1997 Feb; 20(2): 108-11

3. Schaller R, Sperschneider H, Theiler H, Dutz W, Hans S, Voigt D, et al: **Differences in intravenous and subcutaneous application of recombinant human erythropoietin: a multicenter trial.** Artif Organs 1994, Aug; 18(8): 552-8

4. Kaufman-JS; Reda-DJ; Fye-CL; Goldfarb-DS; Henderson-WG; Kleinman-JG;et al: **Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients** N-Engl-J-Med. 1998 Aug 27;

339(9): 578-83

5. De-Schoenmakere-G; Lameire-N; Dhondt-A; Van-Loo-A; Van-der-Goten-J; Duym-P;et al: **The haematopoietic effect of recombinant human erythropoietin in haemodialysis is independent of the mode of administration** (i.v. or s.c.). Nephrol-Dial-Transplant. 1998 Jul;13(7):1770-5

6. Jensen-JD; Jensen-LW; Madsen-JK: **The pharmacokinetics of recombinant human erythropoietin after subcutaneous injection at different sites.** Eur-J-Clin-Pharmacol. 1994; 46(4): 333-7

7. Hussain-R; Naqvi-SA: **Once weekly subcutaneous administration of erythropoietin in haemodialysis patient.** JPMA-J-Pak-Med-Assoc. 1994 Apr; 44(4): 88-90

8. Cheung-WK; Goon-BL; Guilfoyle-MC; Wacholtz-MC: **Pharmacokinetics and pharmacodynamics of recombinant human erythropoietin after single and multiple subcutaneous doses to healthy subjects.** Clin-Pharmacol-Ther. 1998 Oct; 64(4): 412-23

9. Morris-KP; Watson-S; Reid-MM; Hamilton-PJ; Coulthard-MG: **Assessing iron status in children with chronic renal failure on erythropoietin: which measurements should we use?** Pediatr-Nephrol. 1994 Feb; 8(1): 51-6

10. Kooistra-MP; Marx-JJ: **The management of iron metabolism in recombinant human erythropoietin treated dialysis patients by Dutch nephrologists [news].** Nephrol-Dial-Transplant. 1997 May; 12(5): 879-83

11. Markowitz-GS; Kahn-GA; Feingold-RE; Coco-M; Lynn-RI: **An evaluation of the effectiveness of oral iron therapy in hemodialysis patients receiving recombinant human erythropoietin.** Clin-Nephrol. 1997 Jul; 48(1): 34-40

12. Hutchinson-FN; Jones-WJ: **A cost-effectiveness analysis of anemia screening before erythropoietin in patients with end-stage renal disease.** Am-J-Kidney-Dis. 1997 May; 29(5): 651-7.

One should age gracefully not painfully

Mahnaaz Roohi