HUMAN RECOMBINANT ERYTHROPOIETIN IN THE TREATMENT OF ANEMIA OF PATIENTS WITH CHRONIC RENAL FAILURE

Isam Hamo Mahmood[1], Emadeldin Ibrahim Al-badrani[2] & Najlaa Saadi[3]

ABSTRACT

Objective: To compare the effect of small doses of recombinant erythropoietin on anemia of patients with chronic kidney disease who need dialysis and those are not on dialysis.

Design: Case-comparative study.

Setting: Nephrology Department in Al-Salaam Teaching Hospital, Mosul.

Methods: Eighty patients having chronic kidney disease (40 patients needed dialysis and 40 patients needed no dialysis) participated in the study. Epoetin alfa given s.c. in a dose of 4000 IU, 2 times weekly. Hemoglobin was measured before drug administration and every 2 weeks and at the end of the trial period (3 months).

Result: A significant increase of hemoglobin level had been obtained after treatment with erythropoietin in both groups. Comparison between hemoglobin elevation of both groups (3.0 g/l for patients without dialysis and 2.9 g/l for patients with dialysis) revealed a non significant difference (P>0.5).

Conclusion: the present study demonstrated that the administration of epoetin alfa, s.c. in a dose of 4000 IU twice weekly is effective in the elevation of hemoglobin levels in patients with chronic kidney disease. The effect is comparable in patients who need dialysis and in patients who need no dialysis, also the effect is similar in both sexes.

INTRODUCTION

The National Kidney Foundation (NKF) defines chronic kidney disease as kidney damage or a glomerular filtration rate (GFR) of less than 60 ml per minute per 1.73 m^2 (body surface area) for three months or more.[1] This GFR rate corresponds with a serum creatinine concentration higher than 1.5 mg per dl (132.6 μmol per L) in men and higher than 1.3 mg per dl (114.9 μmol per L) in women.[2] More than 20 million people in the United States have stage 2, 3, or 4 chronic kidney disease and do not receive dialysis. More than 320,000 have stage 5 disease, including patients receiving hemodialysis or peritoneal dialysis, or have a functioning renal transplant. Patients who have end-stage renal disease account for more than half a million hospitalizations, averaging 11 days per patient, in the United States each year.[3] It is well recognized that patients with chronic kidney disease have low hemoglobin levels. The etiology of the anemia was eventually determined to be primarily due to the reduction of erythropoietin production and activity.[4] Anemia is defined, according to World Health Organization (WHO) criteria, to be that level of hemoglobin below age- and gender-determined normal ranges. Thus, for males and non-menstruating females, anemia is defined as Hb <13.5 g/dl, while in pre-menopausal women, anemia is defined as a Hb <11.5 g/dl. Using these definitions, a large proportion of patients with chronic kidney disease have anemia, and most dialysis patients remain anemic throughout the course of their dialysis life.[4] The prevalence of anemia in patients with chronic kidney disease prior to dialysis can be determined using population data,[5] and data available from observational studies. Using WHO definitions of anemia, 87% of patients with GFR below 25 ml/min, but not yet on dialysis have anemia.[6] In the current era, 85% of patients are commencing dialysis with Hb levels below 10.0 g/dl.[7] Erythropoietin (EPO), which is produced by the liver in the fetus and by the kidney in the adult, is the primary stimulus of red blood cell formation. A major signal regulating EPO production in these tissues is the oxygen concentration.[8] EPO production is markedly enhanced under hypoxia, mainly through transcriptional activation of the EPO gene. A hypoxia-induced increase of EPO in the blood stimulates the formation of red blood cells, resulting in improvement of the oxygen supply and eventually repression of the activated gene transcription[8]. In normal subjects, plasma EPO levels range from 0.01 to 0.03 Units/ml and increase up to 100-to 1000-folds during hypoxia or anemia.[9] In contrast, in patients with chronic renal failure, production of EPO is impaired, and this EPO deficiency is the primary cause of their anemia.[10] Epoetin alfa (Recombinant human erythropoietin, RHuEpo),

[1]PhD pharmacology, Department of Pharmacology, College of Medicine, University of Mosul, Mosul, Iraq.
[2]MBChB, CABM, Department of Medicine, College of Medicine, University of Mosul, Mosul, Iraq.
[3]M.Sc. Pharmacology, Department of Pharmacology, College of Medicine, University of Mosul, Mosul, Iraq.

a 165 amino acid glycoprotein, manufactured by recombinant DNA technology, has the same biological effects as endogenous EPO. It has a molecular weight of 30,400 Daltons and is produced by mammalian cells into which the human EPO gene has been introduced. The product contains the identical amino acid sequence of isolated natural EPO.[11] RHuEpo has revolutionized the treatment of patients with anemia of chronic renal failure. Moreover, RHuEPO has been shown to be effective in correcting anemia associated with various non-uremic conditions: malignancy, prematurity, HIV infection, post-chemotherapy, post-radiotherapy, post-transplantation, surgery, neuroprotection, critically ill patients and congestive cardiac failure.[12] The presence of other medical problems may affect the use of erythropoietin, causing poor responses including aluminum poisoning, blood clots or other problems with the blood, folic acid, iron or vitamin B12 deficiencies, heart or blood vessel diseases, higher blood pressure, infection, inflammation, cancer, bone problems, sickle cell anemia, seizure, severe hyperparathyroidism, acute or chronic hemolytic conditions, acute or chronic blood loss, and hemoglobinopathies in exceptional instances.[13] Data comparing the effects of erythropoietin on hemoglobin levels in patients with chronic renal disease, who need dialysis and those who need no dialysis using small doses are not available. Thus the aim of this study is to compare the efficacy of epoetin alfa given twice weekly in a dose of 4000 IU, as a treatment of anemia in two groups of patients having chronic renal disease; group 1 those who need dialysis and group 2 those who need no dialysis.

PATIENTS AND METHODS

Eighty patients having chronic renal disease participated in the study. They are divided into two groups. Group one includes 40 patients who need regular dialysis and group two includes 40 patients, who need no dialysis. The patients were collected from Nephrology Department in Al-Salaam Teaching Hospital in Mosul city. All participants completed a consent form, and the study protocol was approved by the Research Ethics Committee. The two groups are sex and age-matched. Each of the two groups consisted of 20 males and 20 females. Patient's age range was 18 to 75 years. Each patient had hemoglobin levels of < 9 g/dl. Major exclusion criteria were; previous EPO treatment, pregnancy or nursing, sepsis or active infection, cancer an anticipated need for renal replacement therapy within 6 months, advanced cardiovascular disease (as defined by a diagnosis of clinically significant valvular disease, congestive heart failure, myocardial infarction, unstable angina, or stroke within the preceding three months), non renal causes of anemia, receipt of blood transfusions within the preceding three months. Epoetin alfa (Product of CHEIL-JEDANG, Vacsera for multipharma, Korea, 2000 IU/0.5 ml) was given s.c. for each patient in a dose of 4000 IU, two times weekly for a period of three months. Hemoglobin was measured before therapy and every two weeks and at the end of the trial period.

Statistical analysis: Paired t-test was used to compare between hemoglobin values at baseline and at the end of three months of both groups. Unpaired t-test was used to compare between hemoglobin elevations in both groups. Level of significance was considered significance at $P \leq 0.05$.

RESULTS

The patients in the two groups were comparable in terms of age and sex shown in As table-1).

Table 1. Patients characteristics.

Parameter	With dialysis	Without dialysis	P-value
Sex	Male 20 Female 20	Male 20 Female 20	
Age (Year)	Mean 48.53±13.79	Mean 51.35±12.96	> 0.2
Hemoglobin at Baseline(g/dl)	Mean 7.73±0.89	Mean 7.70±0.72	> 0.5

Table-2 shows hemoglobin levels before and after treatment with erythropoietin in 40 patients who need no dialysis. A significant increase of hemoglobin levels have been obtained after treatment with erythropoietin.

Table 2. Hemoglobin level before and after treatment with erythropoietin in 40 patients without dialysis (g/dl).

Parameter	Before	After	P-value
Range	6.2-8.8	10-11.5	-
Mean	7.70±0.72	10.70±0.50	< 0.001

Table-3 shows hemoglobin level before and after treatment with erythropoietin in 40 patients who need dialysis. A significant increase of hemoglobin levels have been obtained after treatment with erythropoietin. A comparison between hemoglobin elevation after treatment of both groups (3.0 g/l for patients without dialysis and 2.9 g/l for patients with dialysis) revealed a non significant difference (P>0.5).

Table 3. Hemoglobin level before and after treatment with erythropoietin in 40 patients with dialysis (g/dl).

Parameter	Before	After	P-value
Range	6-9	10-11.3	-
Mean	7.73±0.89	10.63±0.36	< 0.001

(Tables 4 and 5) show hemoglobin blood levels for both males and females of the two groups before and after therapy. A comparison between the elevation of hemoglobin levels between males and females for each group showed no significant differences (P>0.5 for patients with dialysis and P>0.2 for patients without dialysis).

Table 4. Hemoglobin level for males and females before and after treatment with erythropoietin in patients without dialysis.

Parameter	Before	After	P-value
Male	7.65±0.68	10.66±0.52	P <0.001
Female	7.76±0.73	10.65±0.48	P <0.001

Table 5. Hemoglobin level for males and females before and after treatment with erythropoietin in patients with dialysis.

Parameter	Before	After	P-value
Male	7.71±0.84	10.58±0.33	P<0.001
Female	7.76±0.91	10.68±0.38	P<0.001

DISCUSSION

The present study showed that epoetin alfa in a dose of 4000 IU administered twice weekly can significantly increase the Hb blood levels in both groups of patients. The effects were identical in both groups. Patients with chronic renal disease have subnormal endogenous erythropoietin production. Clinical studies have shown that recombinant erythropoietin therapy corrects the anemia of chronic renal failure, avoids blood transfusions and improves quality of life.[14] Furthermore, it optimizes a patient's hemodynamic status thus minimizing the risk of progression to left ventricular hypertrophy and its associated mortality. Furthermore, it leads to an improvement of physical performance and cognitive function.[15,16] Regarding patients with chronic kidney disease who need hemodialysis, RHuEpo have proved in a number of studies to elevate the low hemoglobin levels in such patients.[17-19] Also in pre-dialysis patients previous studies showed that treatment with RHuEPO in pre-dialysis patients corrects anemia and avoids the requirement for blood transfusions.[20,21] Our results were in agreement with results obtained in the above studies. The present study used low doses of erythropoietin (4000 IU twice weekly). A good results were obtained. Our results were in agreement with results obtained in other studies which also used low doses of erythropoiten.[22,23] Was use in the present study used erythropoietin s.c. Many studies showed that Erythropoietin effectiveness is similar after s.c. or i.v. route but s.c route has an advantage over i.v. route in that the dose can be reduced to about 30% to 40%. Horl[24] showed that Patients on haemodialysis who were on i.v. RHuEPO, three times weekly for nine months were subsequently successfully maintained on a self-administered s.c. dosage which was 50% of the i.v. maintenance dosage and which was later reduced further to 30% of the weekly i.v. maintenance dosage. In another study, twelve stable haemodialysis patients were divided into two groups and given recombinant human erythropoietin (RHuEPO) for 14 weeks either intravenously (i.v.) or subcutaneously (s.c.). Dosage was 25 units/kg either thrice (i.v.) or twice (s.c.) per week for seven weeks, and then 50 units/kg for a further seven weeks. Response to s.c. therapy was comparable to i.v. despite a 33% lower weekly dosage.[25] Many

other trials also confirmed that s.c. route lower epoiten alfa dosage requirements compared to i.v. route.[26-29]

In the present study no statistical differences have been obtained between the erythropoietin responses in males or females. Coladonato et al.[30] have defined variable factors that influence epoetin responsiveness and its associated hematocrit response. Male gender, more years on dialysis, older age, use of intravenous iron, and lower serum ferritin were noted to be favorably associated with higher hematocrit levels.

In conclusion, the present study showed that epoetin alfa administered s.c. in a dose of 4000 IU twice weekly is effective in the elevation of hemoglobin in patients with chronic renal disease. The effect is identical in patients who need dialysis and in those who need no dialysis, also the effect is similar in males and females.

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