

THE EFFECT OF RECOMBINANT HUMAN ERYTHROPOIETIN ON ANEMIA OF THE PATIENTS WITH CHRONIC RENAL FAILURE UNDERGOING HEMODIALYSIS TREATMENT

Şükrü SİNDEL, M.D., Enver HASANOĞLU*, M.D., Musa BALI, M.D., Leyla IRAK*, M.D., Turgay ARINSOY, M.D., Ülver BOZTEPE, M.D., Selma FİDAN, M.D.

Gazi University, Faculty of Medicine, Departments of Internal Medicine and Paediatrics*,
Ankara, Turkey
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SUMMARY : *In this study, recombinant human erythropoietin (r-Hu EPO) was administered in a dose of 75U/kg three times a week by subcutaneous route to 38 hemodialyzed patients for three months. After treatment, mean hemoglobin and hematocrit levels increased from 7.55 gr/dl and 24.73 % to 9.75 gr/dl and 31.70 %, respectively. Four patients didn't respond to therapy. One of them had lupus nephritis. The most important side effect was an increment in systolic and diastolic blood pressure values. In conclusion, r-Hu EPO therapy can be used effectively and safely in renal anemia.*

Key Words : *r-Hu EPO, Anemia, Hemodialysis.*

INTRODUCTION

Anemia is one of the main and most consistent clinical manifestations of chronic renal failure. The pathogenesis of the anemia in end-stage renal disease is multifactorial. The main factors contributing to renal anemia are as follows :

- 1- Decreased erythropoietin (EPO) production.
- 2- Inhibitors of erythropoiesis (e.g., spermine, PTH).
- 3- Iron deficiency.
- 4- Aluminum intoxication.
- 5- Decreased red cell survival (hemolysis).
- 6- Excessive blood loss.

The most important cause of renal anemia is a decrement in the production of erythropoietin. Erythropoietin is produced in the peritubular capillary of the cortex and the medulla of kidney (5, 7, 8).

Correction of anemia has been demonstrated in chronically uremic sheep by daily injections of erythropoietin-rich plasma (3). Recent progress in molecular biology has revealed the whole aminoacid sequence of human erythropoietin from the structural gene and has made it possible to produce human EPO in large quantities. Several authors described an increase of hematocrit under treatment with r-Hu EPO.

In order to evaluate the efficiency and safety of r-Hu EPO therapy, this trial was conducted in hemodialysis patients with anemia.

MATERIALS AND METHODS

The study group included 38 patients (26 males, 12 females); mean age 39.3 years (range 5-78) with end-stage renal failure on regular hemodialysis treatment carried out 2 or 3 times a week for 67.8 weeks (range 2-264). Patients with other types of anemia (iron deficiency, hemolysis, autoimmunity, folic acid and B12 deficiency) were excluded from

the study. 8 patients had chronic glomerulonephritis, 2 patients had chronic pyelonephritis, 2 patients had diabetic nephropathy, 2 patients had renal amyloidosis, 1 patient had polycystic disease, 1 patient had lupus nephritis, 1 patient had interstitial nephritis. In 21 patients the underlying disease wasn't known.

r-Hu EPO was administered in a dose of 75U/kg three times a week by subcutaneous route. At the end of the first month, if the increment of hemoglobin (Hb) value was insufficient, r-Hu EPO dose was increased to 125U/kg. The maximum dose was 150U/kg. The estimated target of Hb value was 11 g/dl and the estimated target of hematocrit (Htc) value was accomplished at 35 %.

Before and at the 12 th week of treatment, blood samples were drawn before hemodialysis for Hb, Htc, white blood cell and platelet count. The blood pressures of the patients were recorded before and after the treatment.

Statistical analysis : For the comparison, Student's t test and correlation analysis was used.

RESULTS

Before treatment, the mean was 7.53 g/dl, after treatment of r-Hu EPO it reached 9.75 g/dl, the mean Htc value increased from 24.73 to 31.70 % (Table 1). The increments of mean Hb and Htc values

were statistically significant ($P < 0.001$). The mean white blood cell count changed from 6643.42 to 6512.36. The mean platelet count changed from 226000 to 219684 ($P > 0.05$). No significant differences between pre and posttreatment platelet and white blood cell counts were observed (Table 2).

DISCUSSION

In patients who suffer from chronic renal disease, the production of EPO decreases due to renal damage. Although the ideal treatment of end-stage renal failure associated with anemia is renal transplantation, this is either impossible or unsuccessful in a substantial number of patients who must therefore remain on hemodialysis for long periods of time.

In recent years, renal anemia was corrected successfully by r-Hu EPO (4, 12, 13). Also our study showed similar results.

There are several mechanisms for erythropoietin resistance. These are iron insufficiency, aluminum intoxication, hyperparathyroidism, pyruvate kinase deficiency and chronic inflammatory diseases (9, 10, 14). In our study, four patients didn't respond to therapy. One of them had lupus nephritis. In other cases we couldn't find the cause of EPO resistance.

Approximately one third of hemodialysis pati-

	Before r-Hu EPO treatment	After r-Hu EPO treatment	P Value
	X±SD	X±SD	
Hemoglobin (g/dl)	7.53 ± 1.83	9.75 ± 2.5	< 0.001
Hematocrit (%)	24.73 ± 5.00	31.70 ± 8.24	< 0.001
White blood cell (/mm ³)	6643.42 ± 2571	6512 ± 2081.71	> 0.05
Platelet (/mm ³)	226.000 ± 86.154	219.684 ± 80.240	> 0.05

Table 1 : Mean hemoglobin, hematocrit, white blood cell, and platelet values before and after rHu EPO treatment.

	Before r-Hu EPO treatment	After r-Hu EPO treatment	P Value
	X±SD	X±SD	
Systolic blood pressure (mm/Hg)	128.91 ± 27.05	142.16 ± 27.70	< 0.01
Diastolic blood pressure (mm/Hg)	74.05 ± 16.90	82.97 ± 15.25	< 0.01

Table 2 : Mean blood pressure values before and after rHu EPO treatment.

ents treated with r-Hu EPO experience either an aggravation of preexisting hypertension or develop de novo hypertension. Higher risk of blood pressure increase has been apparent in patients with previous hypertension (2, 4, 6, 11, 12). Normally during EPO therapy; Htc raises, cardiac output lowers and systemic vascular resistancy increases. However if the cardiac output decreases insufficiently, hypertension is inevitable. The factors that increase vascular resistance are high blood viscosity, loss of hypoxic vasodilatation, direct vasoconstrictor effect of erythropoietin, mobilization of vascular cytosolic Calcium, activation of neurohumoral systems and imbalance of local endothelial factors (endothelium derived relaxing factor/endothelin) (1). In our study, we observed significant increments in systolic and diastolic blood pressure values (Table 2).

In an European multicenter study on 150 patients there were 22 occlusions of fistulae within 12 months of r-Hu therapy (12). We observed no clotting problems.

All patients who received r-Hu EPO experienced an increased sense of well being, they were more energetic and able to perform work better, and they looked healthier in general. Some noted an increase in appetite. One patient suffered from itching at the beginning of therapy, but it disappeared without stopping r-Hu EPO treatment. We have observed no other adverse effects.

Successful treatment with r-Hu EPO renders blood transfusion unnecessary. Thus, these patients are no longer exposed to the potential risk of infections such as hepatitis or HIV infection, furthermore there is less likelihood of iron overload and sensitization that may render renal transplantation easier.

In conclusion r-Hu EPO therapy is effective and safe in the treatment of renal anemia.

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Correspondence to : Dr.Şükür SİNDEL
Gazi Üniversitesi Tıp Fakültesi
İç Hastalıkları Anabilim Dalı
Beşevler
06510 ANKARA - TÜRKİYE
Phone : 312 - 212 65 65 / 225