ORIGINAL ARTICLE

Effect of Recombinant Erythropoeitin in Anemia Due to Chronic Renal Failure

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ABSTRACT Recombinant human erythropoeitin (rHuEPO) was administered to 16 patients hospitalized at the Department of Child Health Faculty of Medicine University of Indonesia Cipto Mangunkusumo Hospital between July 1992 until December 1994, with anemia (Hb < 8 g dl) due to chronic renal failure (creatinine uclearance < 30 ml/min/1.3 m^2), three of them with end stage renal failure (creatinine clearance < 5 ml/min/1.73 m^2). The average age was 15.9 years (range 4-16 years) the proportion of sex were the same. An initial dose of 150 IU/kgBW/week rHuEPO was administered subcutaneously. The dose was increased by 75 U/kgBW/week and maintained when the hemoglobin level reached 11 g/di. Good result was mostly found at the dose of 150-199 IU/kgBW/week. The hemoglobin level rose from 6.79 ± 1.19/dl before treatment to 10.4 ± 3.9 g/dl after treatment (p=0.011). Six cases failed to reach Hb 11g/dl, one of them with severe hypertension while in the other case had peritonitis. Decrease of the serum ferritin level during treatment indicated that ferrum was utilized for erythropoesis. This study showed that in chronic renal insufficiency we should consider to give r-HuEPO to increase hemoglobin to avoid giving recurrent blood tranfusion; however, the cost may limit its widespread use. **[Paediatr Indones 1997; 37: 124-131]**

Introduction

Anemia is one of the major complications of renal failure. which leads to the necessity of repeated blood transfusion with its consequent risks and complications. One of the main cause of the anemia in chronic renal failure is the decrease of the production of erythropoeitin.[1-2] Recently, recombinant human erythropoeitin (r-HuEPO) has been

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used in adults receiving hemodialysis and peritoneal dialysis as well as before dialysis, and showed improvement of the anemia.[3-4] Although still rare, recent reports showed that r-HuEPO gave a promising effect in children.[5-6]

The objective of this study was to evaluate the effectiveness and side effects of r-HuEPO in 16 children with anemia due to chronic renal failure treated at the Department of Child Health, Medical School, University of Indonesia-Cipto Mangunkusumo Hospital, Jakarta.

Methods

This one sample pretest-posttest open clinical trial was conducted at the Department of Child Health, Medical School, University of Indonesia-Cipto Mangunkusumo Hospital, Jakarta in 1995. All patients with anemia due to chronic renal failure were entered in this study after parental informed consent. The stages of chronic renal failure were defined as follows:

- chronic renal insufficiency: creatinine clearance 80-25 ml/min/1.73 m^2
- chronic renal failure stage I: creatinine clearance 25-15 ml/min/1.73 m^2
- chronic renal failure stage II: creatinine clearance 15-5 ml/min/1.73 m^2
- end stage renal disease (ESRD) or terminal stage: creatinine clearance < 5 ml/min/1.73 m^2

The inclusion criteria for r-HuEPO administration were: (1) no other causes of anemia, such as thalassemia or sickle cell anemia; (2) anemia due to chronic renal failure with Hb 6-8 g/dl; (3) no persistent severe hypertension; (4) normal liver function.

The drug was administered subcutaneously with a starting dose of 150 IU/kg BW weekly. An increase of hemoglobin level of 1 g/dl per month was a suitable guideline for adequate response. The dose was then titrated by increasing 75 U/kgBW/week and maintained for further 4 successive weeks.

When the target hemoglobin of 11 g/dl was reached the treatment was discontinued. Treatment was considered fail if there was no increase of 2 g/dl at two months, and the hemoglobin level of 11 g/dl was not reached. Laboratory test was done to evaluate hemoglobin status: hemoglobin (Hb), hematocrit level (Ht), serum ferritin, reticulocyte (Rt), differential count. Renal and liver functions, i.e., urea, creatinine albumin, globulin, SGOT, SGPT were also measured. This measurements were recorded as base-line data before treatment. After initiating r-HuEPO Hb, Ht, Rt, were repeated every week, while serum ferritin were re-examined at the end of study. Blood chemistry was evaluated monthly to monitor renal and liver functions and to detect possible side effects.

Iron supplementation was given during treatment to maintain the ferritin level

within normal range. Blood pressure was carefully measured prior to and 30 minutes after r-HuEPO injection, and monitored daily in the hospitalized patients, or weekly in ambulatory patients on follow-up examinations. Other potential side effects were noted during the entire treatment. Wilcoxon signed range test was used for statistical analysis. P value of less than 0.05 was considered to be significant.

Results

During the study period sixteen patients with chronic renal failure consisted of 8 boys and 8 girls with a mean age of 15,9 years (range 14-16) were available for the study (Table 1).

Table 1. Age distribution of patiens

Age (year)	n	Proportion
0-5	3	3/16
6-10	4	4/16
11-16	9	9/16
Total	16	16/16

The etiology of the chronic renal failure was nephrotic syndrome (10 patients) while the others were chronic pyelonephritis, nephritis lupus, and chronic glomerulonephritis (Figure 1). The stages of chronic renal failure among the patients was renal insufficiency in 3 patients (3/16), chronic renal failure stage I in 6 patients (6/16), chronic renal failure stage II in 4 patients, and end stage renal disease (ERSD) in 3 patients (3/16).

The proportion of successful treatment was 10 of 16 patients (Table 2). Good result was found in 5 patients receiving r-HuEPO 150-174 IU/kgBW, 8 patients with the dose of 175 IU/kgBW/week. Only one case received r-HuEPO more than 225 IU/kgBW (Table 3). Good result was found in all 3 cases with renal insufficiency, 3 of 4 cases with stage I chronic renal failure, and 4 of 6 cases with stage II chronic renal failure. No improvement was noted in all 3 cases with ESRD. Hemoglobin level rose from 6.79 $\pm$ 1.19 g/dl before treatment to 10.4 $\pm$ 3.9 g/dl after treatment (Figure 2). " Wilcoxon signed range test showed statistical significance (p:0.0011). The average of the serum ferritin level decreased from 529.25 ng/dl before treatment to 367.18 ng/dl after treatment, indicating that the iron was utilized for erythropoeisis (Figure 3). Severe hypertension was observed in 1 patient so that the drug was discontinued.

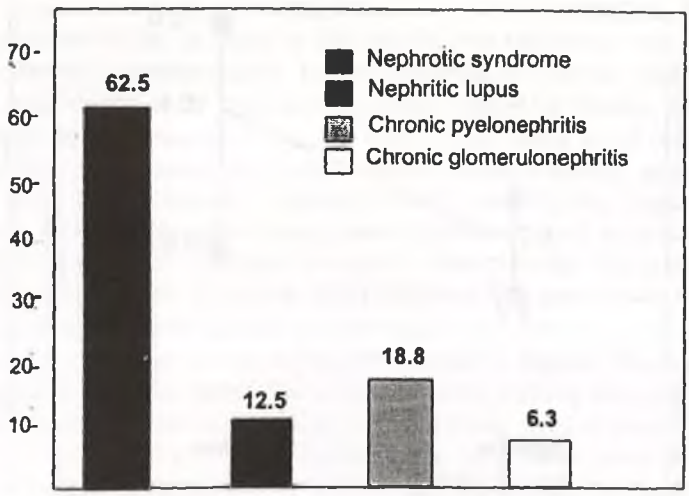

Figure 1. Etiology of chronic renal failure in 16 patients.

Table 2. Proportion of successful treatment of CRF after treatment of r-HuEPO

Result	n	Proportion
Successfull	10	10/16
Failed	6	6/16
Total	16	16/16

Table 3. Distribution of dose of r-HuEPO

Dose IU/kgBW/weeks	n	Proportion
150-174	5	5/16
175-199	8	8/16
200-224	2	2/16
> 225	1	1/16
Total	16	16/16

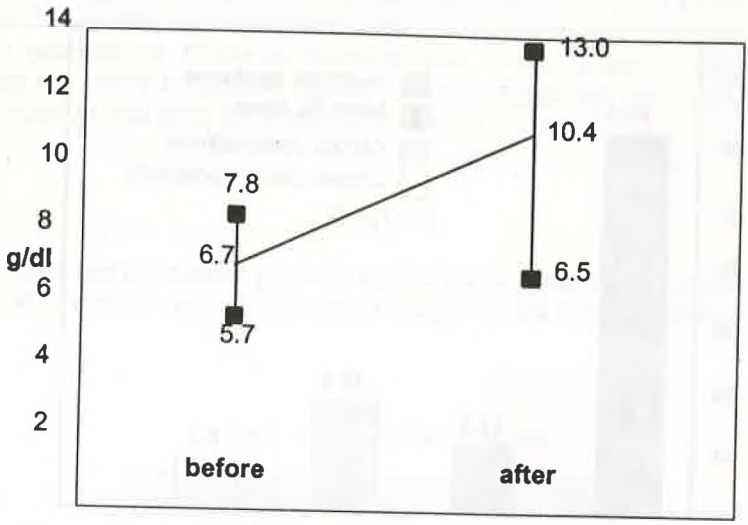

Figure 2. Hemoglobin level before and after treatment r-HuEPO

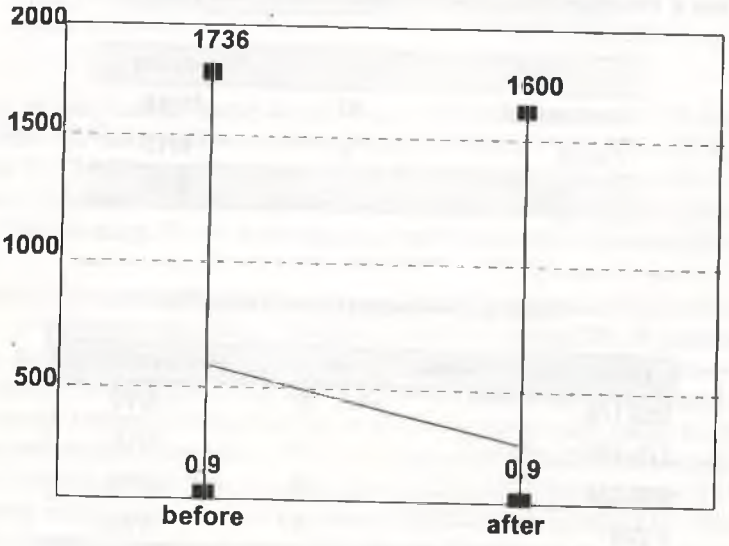

Figure 3. The average of ferritin before and after treatment r-HuEPO

Discussion

The etiology of most of the patients in this study was nephrotic syndrome, while the others were chronic pyelonephritis, lupus nephritis & chronic glomerulonephritis. Broyer *et al*[7] and Habib *et al*[8] reported the major cause of chronic renal failure was congenital renal disease, namely 41% and 43%, while Potter *et al*[9] reported nephrotic syndrome as the main cause of chronic renal failure (42.9%), similar to those of Tambunan[10] and Kristianingesti,[11] namely 33.3% and 72.2%. These diversed data could be due to the different ages among the patients studied. In this study most patients were between 11 and 16 years. Bergstein[2] reported that the primary glomerular disease was the main cause of chronic renal failure at the age of more than 6 years.

The starting dose of erythropoetin in this study was 150 IU/kgBW/week. Best result was found at the dose of 175 IU/kg/BW/week or higher. This finding indicates that the higher the dose the better the result; however further evaluation showed that this condition depended also on the stage of the disease. Several studies have used the average dose between 150 to 199 IU/kgBW/week, 15 to 20% patients needed higher dose than 150 IU/kgBW/week and sometimes 300 IU/kgBW was needed.[3]

In this study most of the patients were in chronic renal failure, while 3 patients had ESRD. The success of treatment was associated with the stage of the disease; there was a tendency that in the later stage rHu-EPO gave the worse result; in ESRD no patient responded the treatment. The reason to support this condition is that in later stages the destruction of renal parenchyma is more prominent so that the production of erythropoeitin is lower.[12] Besides that, in chronic renal failure a hemolytic factor also plays a role in the development in anemia, which according to Giovanetti[13] is due to methyl guanidine.

This study demonstrates that subcutaneous r-HuEPO was effective to increase hemoglobin (from the mean of 6.79 g/dl to 10.4 g/dl), (p=0.0011). Several studies have confirmed the efficacy of r-HuEPO in improving anemia in end stage renal failure as well as in patients not yet requiring dialysis therapy. Lim[14] treated 14 anemic patients with intravenous r-HuEPO in a double blind placebo-controlled trial and reported an increase in mean hemoglobin levels from 9.1 $\pm$ 0.2 g/dl to 12.3 $\pm$ 0.4 g/dl over a 2-month period. Esbach had administered r-HuEPO in 17 predialysis patients with anemia and observed a median rise of hematocrit from 27 vol% to 37 vol%.[15]

It is important to measure the serum iron level in patients treated with r-HuEPO. In patients with iron deficiency, indicated by a low level of serum ferritin level, ferrum should be supplemented either orally or parenterally in conjunction with r-HuEPO. This study shows that all patients given r-HuEPO showed a decrease of serum ferritin needed for the production of erythrocytes in the bone marrow. One patient with low level of serum ferritin at the beginning of the study was supplemented with ferrum. Ferrous sulfate was recommended to be administered orally even in patients with normal serum ferritin level; patients with depleted iron levels can develop iron deficiency

under influence of r-HuEPO.[16]

Partial correction with r-HuEPO is the best treatment for patients with anemia in chronic renal failure. A linear increase in the hemoglobin level leads to an exponential rise in whole body viscosity.[12] which is thought to contribute to many side effects in r-HuEPO therapy, such as hypertension, increased peripheral resistance, and thrombotic complication.[12]

Based on the above consideration a rise of 1 g/dl in 4 weeks appears to be the best compromise and the optimum target of hemoglobin level to be in a range of 10-12 g/dl.[17] The target Hb level in this study was set at 11 g/dl, as the end point of the r-HuEPO titration dose, to minimize possible complications of treatment.[17,18] In this study only one patient developed severe hypertension; no other side effect was observed. Hypertension is indeed the most frequently reported side effect associated with r-HuEPO therapy.[18] Results of multicenter clinical trials involving 309 patients show that 72% patients with existing hypertension are in no greater risk of acquiring increased blood pressure than those who are normotensive at the beginning of treatment. Only 39% of the patients are reported as having a rise of blood pressure of 10 mmHg or more.[17] The increase blood pressure in r-HuEPO therapy is thought to be mediated by a number of pathophysiologic changes, namely increased blood viscosity, increased peripheral resistance, and failure in reducing the elevated cardiac output due to anemia.[17,18]

To sum up, data of this study have shown that r-HuEPO has a promising effect in increasing the hemoglobin level in children with anemia due to chronic renal failure. However, the expensive cost of the drug may limit its use in developing countries.

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