

Original Articles

RECOMBINANT HUMAN ERYTHROPOIETIN IN THE TREATMENT OF ANEMIA IN CHILDREN

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ABSTRACT

We have used recombinant human erythropoietin (r-HuEPO) in children with chronic renal failure. There was significant improvement in anemia and well-being, along with regression of left ventricular mass and no change in the rate of decline of renal function. It is safe and effective in the pre-dialysis as well as the hemodialysis period. Considering the benefits of r-HuEPO, transplantation in children can be postponed to a later time, when sufficient growth and development have occurred, leading to better results of transplantation.

Keywords: Recombinant human erythropoietin, Chronic renal failure, Predialysis, Hemodialysis
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INTRODUCTION

Anemia, which is primarily due to a decrease in erythropoietin (EPO) production, is a common finding in chronic renal failure (CRF). Until a few years ago, many of these patients required blood transfusions with the associated risk of sensitization to histocompatibility antigens, hepatitis, and iron overload. Multi-center trials of EPO in adult patients with end stage renal disease have demonstrated the effectiveness of r-HuEPO.^{1,2} Experience with r-HuEPO in pediatric patients has also been reported.^{3,4} This is a trial of r-HuEPO among children with CRF in Iran, comparing its effect on pre-dialysis patients and patients on dialysis.

PATIENTS AND METHODS

Twenty children with CRF of various etiologies, ten on hemodialysis and ten patients before dialytic therapy were included in this study. Five females and five males were

included in each group, with an age range of 1.5 to 12 years. The study period was three months which was preceded by a three-month control period. All patients had a hematocrit of less than thirty percent (30%). Patients with evidence of hemorrhage, documented by stool exam and reticulocyte count were excluded. All had normal serum iron, TIBC, vitamin B₁₂, liver function tests, folic acid, and no evidence of pulmonary infection by chest X-ray. All had negative urine cultures and were hepatitis B surface antigen negative. Only one patient was hypertensive.

r-HuEPO was administered subcutaneously for all patients. In five of the patients on dialysis, it was given in a dose of 50 U/kg, and in the other five, it was administered in a dose of 100 U/kg, half an hour prior to dialysis, twice weekly. Five of the predialysis patients were treated with 100 U/kg once a week, and five were treated with 50 U/kg twice weekly. The hemoglobin, hematocrit, reticulocyte count, blood urea nitrogen, creatinine, calcium, phosphorus, and electrolytes were monitored prior to treatment and every one to two weeks; liver function tests, PTT, PT, and

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Table I. LVIDd* changes with EPO therapy (pre-dialyzed patients).

Patient No.	Pre-Rx Mean LVIDd	Post-Rx Mean LVIDd	P
1	31.7±2.5	26.8±1.2	<0.01
2	30±1.7	28.7±1.7	NS
3	37.7±1.7	35.8±1.2	NS
4	34.8±1.2	32±1.7	<0.02
5	37.6±1	35±2	NS

*LVIDd: Left ventricular intra-diastolic dimension.

Table II. LVIDd changes with EPO therapy (hemodialyzed patients).

Patient No.	Pre-Rx Mean LVIDd	Post-Rx Mean LVIDd	P
1	40.2±1.7	42.3±1.1	NS
2	40±3.7	42.6±2.2	NS
3	44±2.2	44.8±1.2	NS
4	38.7±1.9	37±1.7	NS
5	39.8±1.2	38±1.2	<0.05

cultures were monitored each month. Electrocardiography and echocardiography were obtained prior to and after treatment for five patients in each group.

RESULTS

All patients required at least one transfusion in the control period, but there was no need for transfusion during the treatment period, except for one of the hemodialyzed patients. The decreasing need for transfusion in the treatment period was significant ($2.6±1.2$ vs. $0.2±0.4$; $p<0.05$). In patients on hemodialysis, the hematocrit increased significantly after treatment ($21.15±2.94$ vs. $26.89±2.6$; $p<0.05$) (Fig. 1). In predialysis patients also hemoglobin and hematocrit values showed a significant rise with r-HuEPO ($22.14±2.65$ vs. $29±3.67$; $p<0.01$) (Fig. 2). The reticulocyte count also increased following treatment ($0.27±0.6$ vs. $2.1±0.79$; $p<0.001$) (Figs. 3,4). There was an increase in weight and sense of well-being among forty per cent of the patients. Kidney function did not change significantly in any of the patients during treatment.

Echocardiographic evidence of a decrease in left ventricular intra-diastolic dimension (LVIDd) was observed in all predialyzed patients, with a significant change in two of the patients (Table I) and among one of the hemodialyzed patients (regression was observed in one patient, Table II). Significant changes in interventricular septum in diastole

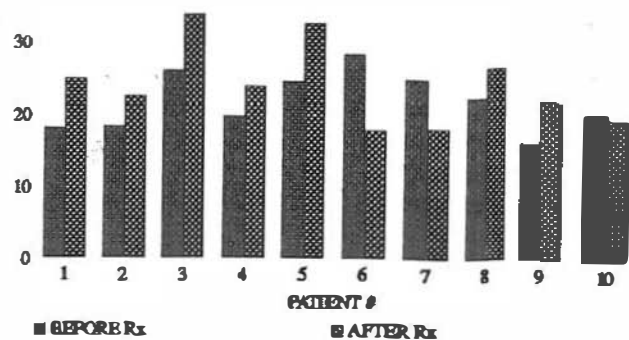


Fig. 1. Hematocrit changes in dialyzed patients.

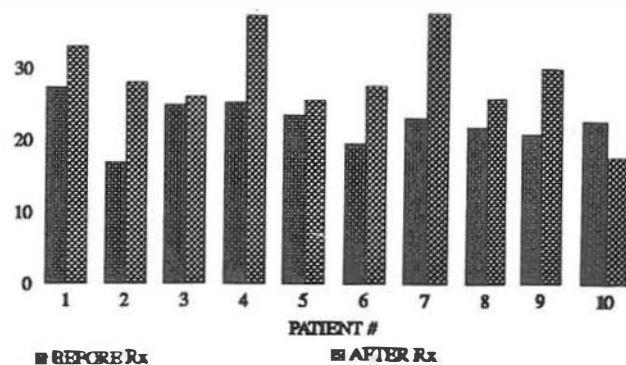


Fig. 2. Hematocrit changes in non-dialyzed patients.

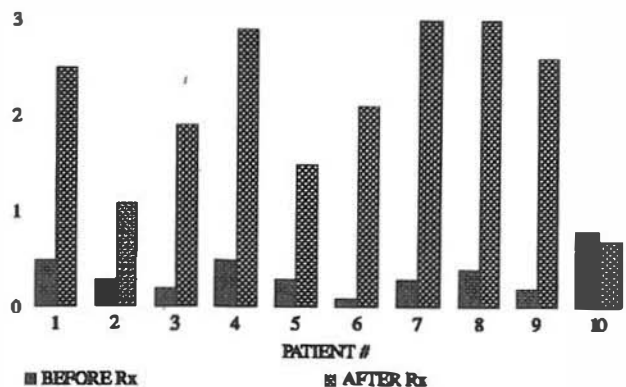


Fig. 3. Reticulocyte changes in dialyzed patients.

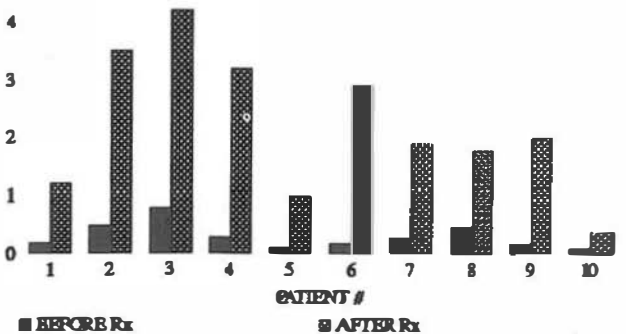


Fig. 4. Reticulocyte changes in non-dialyzed patients.

Table III. IVSd* changes with EPO therapy (hemodialyzed patients).

Patient No.	Pre-Rx Mean IVSd	Post-Rx-Mean IVSd	P
1	11.0±0.9	10.0±0.0	NS
2	10.0±1.0	10.6±0.8	NS
3	17.0±1.2	16.6±1.9	NS
4	12.2±1.2	10.6±0.5	<0.05
5	13.2±1.0	10.8±0.4	<0.01

*IVSd: Interventricular septum dimension.

Table IV. Left ventricular mass changes with EPO Rx.

Patient No.	Non-dialyzed			Dialyzed		
	Pre-Rx	Post-Rx	% Change	Pre-Rx	Post-Rx	% Change
1	99	70.5	-29	226	255	+13
2	132	108	-18	150	178	+20
3	177	131	-26	354	285	-20
4	178	112	-37	162	125	-30
5	206	185	-11	214	170	-20

(IVSd) were observed in three dialysis patients (Table II). Decrease of left ventricular mass was observed in all predialyzed patients and among three of the dialyzed patients (Table IV). New-onset hypertension was observed in only one patient. There were no vascular or thrombotic complications, no adverse changes in biochemical parameters, and no acceleration in rate of decline of renal function.

DISCUSSION

Our observations point to effective results with EPO therapy in children suffering from renal failure, correcting the anemia, enhancing well-being, improving appetite and activity, and decreasing the need for transfusion; these findings have also been noted by others.^{1,6} Once a week administration is feasible, with increased patient compliance and reduced cost of treatment.⁷ Subcutaneous administration of EPO was without any major side-effects, particularly hypertension, probably due to slow rise in hemoglobin levels, especially in the predialysis group.⁸

Decrease of left ventricular intra-diastolic dimension was observed in fifty per cent of dialyzed patients and a decrease in interventricular septum dimension in sixty per cent of predialyzed patients. Regression of left ventricular mass was noted among one hundred percent of predialyzed

and sixty percent of dialyzed patients; this can be one of the most beneficial effects of treatment in each group, particularly in predialyzed patients; partial regression has been observed in dialyzed patients by others.^{7,9}

Treatment by EPO did not accelerate the rate of decline of residual renal function; however, longer periods of study are needed for a firm conclusion in this regard. Longer periods of therapy, with control of hypertension and correction of anemia, have not altered progression of the original renal disease.^{10,11}

We believe, therefore, that EPO is effective for correction of anemia and prevention of cardiac complications. In children, longer periods of EPO treatment and better correction of anemia can lead to a better pre-transplantation condition; this possibility needs further investigation.

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