Enteral Erythropoietin Increases Plasma Erythropoietin Level in Preterm Infants: A Randomized Controlled Trial

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Abstract

Objective: *To evaluate the effects of enteral administration of recombinant human erythropoietin (rhEPO) on serum level of erythropoietin and erythropoiesis in preterm infants.* ***Study design:*** *Randomized controlled trial.* ***Setting:*** *Level III NICU.* ***Subjects:*** *16 preterm infants less than 34 wk with birth weight less than 1800 g.* ***Intervention:*** *Enteral rhEPO 400 U/kg, three times/week, plus $FeSO_4$,3-6 mg/Kg/day (Study group, n = 7) or $FeSO_4$ only (Control group, n = 9).* ***Outcome measures:*** *Hemoglobin, serum erythropoietin (EPO), reticulocyte count, and serum ferritin levels, measured at baseline, after 10 days and at discharge.* ***Results:*** *Mean birth weight and gestational age for the Study and the Control groups were 1328.5 ± 267.4 vs. 1392.8 ± 196.7 g and 30.7 ± 2.5 vs. 30.2 ± 0.9 weeks, respectively. At discharge, there was no difference in hemoglobin or hematocrit but the reticulocyte counts were significantly higher in the Study group (1.4 ± 0.7 vs. 0.7 ± 0.4, P = 0.03). Serum erythropoietin level was significantly higher in the Study group (18 ± 11 vs. 8.6 ± 3.9 mU/mL, P = 0.006). Conversely, serum ferritin level was lower in the study group but did not achieve statistical significance.* ***Conclusions:*** *Enteral administration of rhEPO in preterm infants resulted in increase in serum erythropoietin and reticulocyte counts at the time of discharge without significantly affecting hemoglobin or hematocrit.*

Key words: *Erythropoiesis, Preterm, rhEPO.*

Introduction

Anemia is very common in very low birth weight (VLBW) infants(1,2). It may become severe enough to require red blood cells transfusion. This has been related to blood letting for laboratory analysis and hyporegenerative state of the bone marrow secondary to erythropoietin (Epo) deficiency(1). Recombinant form of erythropoietin or rhEPO became available in mid 1980's. In VLBW infants, randomized clinical studies with parenteral rhEPO, has been shown to maintain a stable hematocrit and decreased the need for red blood cells transfusion(1-5). While parenteral rhEPO has been shown to enhance erythropoiesis and decrease the need for late blood transfusion in preterm infant, the effects of its enteral administration provided conflicting results(6-10). We report the results of our study evaluating the effects of enteral rhEPO on erythropoiesis in stable preterm infants.

Methods

Preterm infants with birth weight less that 1800 g and gestational age less than 34 weeks were enrolled and sequentially openly randomized. Additional criteria for eligibility were stable cardiopulmonary status for at least 7 days and enteral feeding of at least 50 mL/kg/day of human milk. Infants with congenital anomalies, grade III and IV intracranial hemorrhage, seizures, immune-mediated hemolytic anemia and evidence of acquired and congenital infection were excluded. The Study group (n = 7) received three times weekly enteral administration of 400 U rhEPO, added to breast milk, and daily administration of enteral $FeSO_4$ 3-6 mg/kg/day until

discharge. The Control group ($n = 9$) received only enteral $FeSO_4$. Complete blood count, reticulocyte counts (corrected with hematocrit), serum erythropoietin (enzyme linked immunosorbant assay, Gamma Counter Clin, LKB Company, Germany) and serum ferritin (quantitated by radioimmuno-assay, Immunotec Company, France) levels were measured at the day of entry; 10 days post initiation of the study and on the day of discharge. All the babies were fed human milk. Adverse events such as feeding intolerance, necrotizing enterocolitis, circulatory instability, temperature instability, thrombocytopenia and leukopenia were recorded. Data were analyzed utilizing SPSS software. Study and Control groups were compared by *t*-test for repeated measures because the distribution of outcome variables was normal according to Kolmogorov-Sminoroff test. Our institutional review committee for ethical research approved the study. Written informed consent from parents was obtained prior to enrollment of the subjects in the study.

RESULTS

Clinical characteristics of the Study and the Control group are shown in ***Table I***. There were no difference in birth weight, gestational age and the day of enrollment in the study between the Study and the Control group. The Study group received rhEPO from the day of enrolment to discharge. They received rhEPO for 25 ± 10 days (range 15-35 days). Two subjects from the Control group developed recurrent apnea and septicemia. Based on clinical assessment, they were given red blood cells transfusion. They were excluded from further data analysis. No subject from the study group required red blood cells transfusion. No other significant adverse event was noted in the remaining control subjects or in the study group. ***Table II*** shows comparative hematologic status, serum erythropoietin and serum ferritin levels between Study and Control group. Reticulocyte counts and serum erythropoietin levels were significantly higher in the Study group after 10 day of rhEPO treatment and at discharge. There were no significant differences in serum ferritin level, hemoglobin and hematocrit between the groups after 10 days of therapy or at discharge.

DISCUSSION

The results of our study are similar to two previous studies using enteral rhEPO. Ballin, *et al.*(10) using 600 U/kg/week enteral rhEPO, in 3 divided doses, showed significantly higher reticulocyte response and significantly higher serum erythro-poietin levels. Britton *et al*.(9), using 1000 U/kg/10 days of enteral rhEPO, measured serum erythro-poietin at several time intervals. Similarly, these investigators also showed significantly increased serum erythropoietin levels and accelerated erythropoiesis. Both parenteral as well as the enteral use of rhEPO may result in serum ferritin level to decrease as noted by Ballin, *et al*.(10) and Kling and Winzerling(11). Compared to the Control, our Study group had decreased serum ferritin levels with rhEPO therapy but the values did not achieve statistical significance.

In order for the enteral rhEPO to have erythropoietic effect on bone marrow, it has to stay stable in the gastrointestinal tract, particularly in the acidic milieu of the stomach and be absorbed intact from the gastrointestinal tact and reach the bone marrow. Juul, *et al*.(8,12) and Kling, *et al.*(7) have shown that rhEPO added to human milk remains

TABLE I DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN TWO GROUPS

Parameter	Study group ($n = 7$) Mean ± SD	Control group ($n = 9$) Mean ± SD	*P* value
Gestational age (wk)	30.7 ± 2.5	30.2 ± 0.9	0.67
Birth weight (g)	1328.5 ± 267.4	1392.8 ± 196.7	0.21
Weight at enrolment (g)	1242.8 ± 265.2	1357.1 ± 205.0	0.38
Age (d)	15.1 ± 5.3	15.4 ± 3.7	0.91

intact under physiologic digestion conditions. In suckling rat pups, 8 to 10% of total enterally administered rhEPO dose was localized to bone marrow, percentages comparable to those seen after parenteral administration(8). Contrary to the findings by Britton, *et al*.(15) and Ballin, *et al*.(10), showing increased serum erythropoietin levels and significant increase in reticulocyte counts with enteral administration of rhEPO, a randomly assigned study in VLBW infants by Juul(6), administering 1000 U/kg of enteral rhEPO for 14 days versus control, failed to show significant increase in serum erythropoietin or a substantial increase in reticulocyte count after 7 and 14 days of treatment.

Additional benefits of parenteral and enteral rhEPO may be the trophic and maturation effects of the gastrointestinal tract immunity(13,14), decrease in the incidence of necrotizing enterocolitis(15), neuroprotection and modification of signal transduction systems regulated by erythropoietin in the nervous system(16). The early administration of parenteral rhEPO for preventing red blood cell transfusion in preterm and/or low birth weight infants was recently reviewed by Ohlsson and Aher as part of the Cochrane review(17). Review of 23 studies with enrollment of 2074 preterm infants, revealed that parenteral rhEPO administration, while reduced the need for red blood cells transfusion, significantly increased the incidence of retinopathy of prematurity, a serious complication that may cause blindness. In our study of a small number of VLBW infants, we did not note any significant adverse effect. Caution should be used for the indiscriminate use of enteral rhEPO in VLBW infants.

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TABLE II HEMATOLOGIC PARAMETERS IN TWO GROUPS

Variable	Time	Study group ($n = 7$) Mean ± SD	Control group ($n = 7$) Mean ± SD	*P* value
Hematocrit (%)	0	32.9 ± 9.6	34.3 ± 9.7	0.30
	10 day	26.4 ± 5.5	30.6 ± 7.7	
	end	21.3 ± 1.9	24.8 ± 5.9	
Hemoglobin (g/dL)	0	9.9 ± 4.8	11.5 ± 1.5	0.17
	10 day	8.4 ± 2.0	10.4 ± 3.0	
	end	6.8 ± 1.0	8.4 ± 1.8	
Reticulocyte (%)	0	0.5 ± 0.3	0.4 ± 0.1	0.03
	10 day	0.7 ± 0.3	0.3 ± 0.2	
	end	1.4 ± 0.7	0.7 ± 0.4	
Ferritin level (μg/L)	0	404.8 ± 104.3	242.8 ± 76.2	0.41
	10 day	373.4 ± 246.2	286.0 ± 60.7	
	end	238.0 ± 78.1	340.7 ± 166.5	
Epo level (mU/mL)	0	5.9 ± 3.8	3.3 ± 3.7	0.006
	10 day	8.1 ± 5.9	4.9 ± 2.3	
	end	18.0 ± 11	8.6 ± 3.9	

WHAT IS ALREADY KNOWN?

- Parenteral administration of recombinant erythropoietin has been shown to enhance erythropoiesis and decrease the need for late blood transfusion in preterm infants.

WHAT THIS STUDY ADDS?

- Enteral administration of recombinant erythropoietin in preterm infants results in increase in serum erythropoietin, without significantly affecting hemoglobin, within a short follow-up period.

design, data collection, analysis and drafting of the manuscript.

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