ARTICLE

Comparison of 2 Iron Doses in Infants Receiving Recombinant Human Erythropoietin Therapy

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Objective: To compare iron sufficiency in premature infants receiving high-dose recombinant human erythropoietin (r-HuEPO), 1200 IU/kg per week, supplemented with 6 or 12 mg/kg per day of enteral iron.

Design: We conducted a prospective, double-blind, controlled study of premature infants receiving r-HuEPO therapy, randomly assigned to receive 2 different doses of iron. Measurements of ferritin, iron, total iron-binding capacity, reticulocyte count, hemoglobin level, and hematocrit were obtained at baseline, 4, and 6 weeks. Transferrin saturation was calculated; the number of blood transfusions and the incidences of sepsis were recorded.

Setting: This study was performed in the neonatal intensive care unit at Loma Linda University Children's Hospital, Loma Linda, Calif.

Subjects: Infants with a gestational age of 32 weeks or younger, older than 7 days, and receiving r-HuEPO therapy from March 1, 1997, to June 30, 1998, were eligible for the study. Infants were randomly assigned to receive 6 mg/kg per day or 12 mg/kg per day of enteral iron during a course of r-HuEPO therapy for 4 to 6 weeks.

Results: Sixty-four infants were enrolled in the study. Twelve infants did not complete the study; 52 completed 4 weeks and 41 completed 6 weeks of the study. While ferritin levels and transferrin saturation decreased in both groups over the study period, there were no differences between the 2 study groups.

Conclusions: Infants receiving high-dose r-HuEPO therapy (1200 IU/kg per week) decrease their ferritin levels (measure of iron stores) even when receiving high enteral iron supplementation. Given that the ferritin levels were similar between the 2 groups, we speculate that the additional iron either was not absorbed or was not stored.

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INADEQUATE ERYTHROPOIETIN levels are a major factor in the cause of anemia of prematurity.[1-7] Recombinant human erythropoietin (r-HuEPO) is used frequently to treat anemia of prematurity and has been shown to increase the reticulocyte count, hemoglobin level, and hematocrit and to decrease the number and volume of erythrocyte transfusions in premature infants.[8-13] Different doses of r-HuEPO have been evaluated by various clinical trials. The combination of r-HuEPO and iron supplementation has been shown to enhance erythropoiesis in premature infants compared with giving r-HuEPO alone.[14] The erythropoietic response is dose-dependent[12] and a significant reticulocyte response with increased hematocrit has been obtained using high-dose r-HuEPO therapy (1200 IU/kg per week).[15] We routinely use this high-dose of r-HuEPO in our neonatal intensive care unit to maximize erythropoiesis.

Increased erythropoiesis depletes the body iron stores.[13,16] Erythropoietin use in animal models decreases plasma, hepatic, cardiac, and skeletal muscle iron stores.[17] A similar decrease in iron content has been found in the liver, heart, and brain of infants having augmented erythropoeisis and who were born to mothers with diabetes mellitus.[18] Use of r-HuEPO therapy in humans causes a significant fall in the serum ferritin level, a major indicator of iron stores.[13,16,19] Most clinical studies in newborn infants use serum ferritin to assess iron stores because it is impractical to perform invasive procedures such as liver or bone marrow biopsies.[20-24] Serum iron level, transferrin saturation, and total iron binding capacity (TIBC), less sensitive indicators of iron sufficiency, are also affected and inversely related to the r-HuEPO dose.[11]

The ideal amount of iron supplementation while receiving r-HuEPO is unknown. In an early study, Shannon[10] administered 6 mg/kg per day of iron enterally during r-HuEPO therapy (500 IU/kg per week). Other studies have also used 6 mg/kg per day of enteral iron dur-

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SUBJECTS AND METHODS

To determine iron sufficiency for premature infants receiving erythropoietin therapy, we designed a prospective, randomized study to evaluate the effects of 2 different doses of enteral iron supplementation in premature infants who were receiving 1200 IU/kg per week of r-HuEPO (the standard dose used in our unit for such infants). Recombinant human erythropoietin (Epoetin Alfa; Amgen Inc, Thousand Oaks, Calif) was administered either intravenously, if access was available, or subcutaneously. The randomization code was developed using a computer random number generator to select random permuted blocks. The block lengths of 4 and 6 were randomly varied. The hospital pharmacist assigned infants to receive enteral iron as ferrous sulfate (Mead Johnson Pharmaceuticals, Indianapolis, Ind) at 6 mg/kg per day or 12 mg/kg per day. The enteral iron supplements were prepared in the pharmacy and placed in syringes with the actual dose concealed from the caregivers and investigators.

We used the levels of serum ferritin and serum iron, as well as the TIBC to determine the status of iron stores. Transferrin saturation was calculated for each infant at each study time point. Reticulocyte count, hemoglobin level, hematocrit, incidence of sepsis, and the number and volume of erythrocyte transfusions were recorded as secondary variables. These tests were performed at baseline and were repeated at 4 and 6 weeks. This study was approved by the institutional review board of Loma Linda University Children's Hospital, Loma Linda, Calif. Parental consent was obtained.

SUBJECT SELECTION

All infants admitted to the neonatal intensive care unit at Loma Linda University Children's Hospital with a gestational age of 32 weeks or younger, older than 7 days of life, and receiving r-HuEPO therapy were eligible to be enrolled in this study. Infants were excluded from the study if, at the time of enrollment, they had a contraindication to receive enteral iron supplementation (eg, feeding intolerance). Infants were removed from the study if they developed gastrointestinal symptoms precluding enteral intake for longer than 10 days.

PROTOCOL

Infants were randomized to receive 6 or 12 mg/kg per day of enteral iron, starting when they were tolerating a minimum of 50 mL/kg per day of enteral feedings. Iron supplementation was begun within 10 days of the initiation of r-HuEPO therapy. Infants were studied at baseline and at 4 weeks. Additional measurements were obtained for infants who remained hospitalized at 6 weeks. The caregivers were masked to the iron dosage and provided routine neonatal care.

The total quantity of blood drawn and transfused during the study was recorded and compared between the 2 groups. Clinicians caring for infants ordered erythrocyte transfusions without consulting the investigators. Infants were transfused based on written guidelines developed for our neonatal intensive care unit based on the criteria of Shannon et al.[9]

LABORATORY ANALYSIS

Ferritin levels were measured using microparticle enzyme immunoassay technology (Abbot AxSYM; Abbott Laboratories, Abbott Park, Ill). Iron and TIBC levels were determined using a timed endpoint method (Beckman Synchron CX4CE; Beckman Coulter Inc, Fullerton, Calif). Reticulocyte count was performed using a flow cytometry technique argon laser (avamine-o-dye) fluorescence (Sysmex-R-3000; Roche Diagnostics). Hemoglobin and hematocrit values were measured using a modification of the manual cyanmethemoglobin method (Advia 120; Bayer Diagnostics, Tarrytown, NY).

STATISTICAL ANALYSES

A sample size of 27 infants in each group was calculated to detect a 40% difference in the plasma ferritin level with an α level of .05 and 80% power. This sample size would be insufficient to detect smaller differences. Statistics were calculated using SPSS for Windows, Version 10 (SPSS Inc, Chicago, Ill). Demographic statistics were calculated to define the infant population. χ^2 Test was used to analyze the incidence of sepsis and to compare the numbers of transfusions. Mann-Whitney test was used to compare differences for age at the start of study and blood volume both withdrawn and transfused. Two-way analysis of variance for repeated measures was used to compare the values of serum ferritin, serum iron, TIBC, reticulocyte count, and hematocrit over the course of the study between the 2 iron supplementation groups.

ing r-HuEPO therapy.[8,9,25-27] Based on the findings from these studies, it has been the practice in our neonatal intensive care unit to administer 6 mg/kg per day of enteral iron for infants receiving r-HuEPO therapy. Considering the potential of r-HuEPO therapy to cause iron deficiency and recognizing that we use a high-dose of r-HuEPO, we wished to determine a sufficient but not excessive iron supplementation dosage.[15] Therefore, we designed a study to evaluate iron sufficiency in premature infants receiving high-dose r-HuEPO supplementation at a dosage of 6 mg/kg per day of enteral iron (our standard dose) vs 12 mg/kg per day of enteral iron. We hypothesized that using a higher dose of enteral iron supplementation would prevent functional iron deficiency (iron being unavailable for incorporation into the erythrocytes) and enhance erythropoiesis in premature infants treated with r-HuEPO. We selected the higher dose of iron expecting to provide sufficient iron for the high dose of r-HuEPO used, but not so high a dose as to risk the toxic effects of iron or gastrointestinal intolerance.

RESULTS

Sixty-four infants of 32 weeks' gestational age or younger were enrolled between March 1, 1997, and June 30, 1998. Infants were randomly assigned to receive either 6 mg/kg per day or 12 mg/kg per day of iron supplementation. Twelve infants were excluded from the study before the fourth week (3 from the 6 mg/kg per day iron group and 9 from the 12 mg/kg per day iron group). One infant from the 6 mg/kg per day iron group was excluded due to necrotizing enterocolitis. Two infants (1 from each iron dos-

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Demographic Values and Characteristics of the Study Population*

Variable	Iron Dose Group: 6 mg/kg per Day	Iron Dose Group: 12 mg/kg per Day
No. of infants completing		
4 wk (n = 52)	29	23
6 wk (n = 41)	23	18
Birth weight, g†	990 (350)	1120 (360)
Gestational age, wk†	27 (2)	28 (2)
At start of study		
Age, d‡	24 (242)	16 (23)
Weight, g†	1273 (364)	1300 (500)
Hematocrit, %	35.7 (4.3)	36.4 (3.9)
During the study		
Mean change in weight, g	1336 (712)	1146 (582)
Blood volume		
Withdrawn, mL‡	27 (51)	20 (50)
Transfused, mL/kg‡	0 (50)	0 (30)

*Data are given as mean (SD) unless otherwise indicated. Patients were given recombinant human erythropoietin either intravenously or subcutaneously.
†Mean (SD) for infants who completed 4 weeks of the study.
‡Data are given as median (range).

age group) were excluded due to feeding intolerance. Nine of the 12 infants (8 from the 12 mg/kg per day iron group and 1 from the 6 mg/kg per day iron group) exited the study owing to hospital discharge to home prior to 4 weeks. These 9 infants had similar baseline hematocrit values, discharge weights, and gestational ages when compared with the infants discharged after 6 weeks. Six of those 9 infants had an increase in hematocrit from baseline prior to their discharge while 3 had a decrease in hematocrit. Thus, 52 infants completed 4 weeks of study, 29 in the 6 mg/kg per day iron group and 23 in the 12 mg/kg per day iron group. Forty-one of the 52 infants completed 6 weeks of the study, 23 in the 6 mg/kg per day iron group and 18 in the 12 mg/kg per day iron group. There were no significant differences between the 2 iron supplementation groups at enrollment for birth weight or gestational age. There were no differences at the start of the study for age, weight, or hematocrit. There was no difference in weight at the end of the study (**Table**).

Serum ferritin levels decreased significantly from baseline during the r-HuEPO course in both the 6 mg/kg per day and the 12 mg/kg per day iron groups ($P<.001$) at 4 and 6 weeks. There was no statistical difference between the 2 iron supplementation groups (**Figure 1**). The serum iron level and TIBC did not show any significant difference either in time sequence or between groups during the r-HuEPO course. Transferrin saturation decreased significantly over time ($P<.007$), but the difference between the 2 iron supplementation groups was not statistically significant (Figure 1). Additionally, there was no statistical difference in volume of blood drawn or transfused between the 2 iron supplementation groups during the study (Table 1).

Infants in both groups had similar hematocrits at baseline and maintained steady values throughout the study. There was no difference in hematocrits between the groups at 4 weeks and 6 weeks of r-HuEPO therapy.

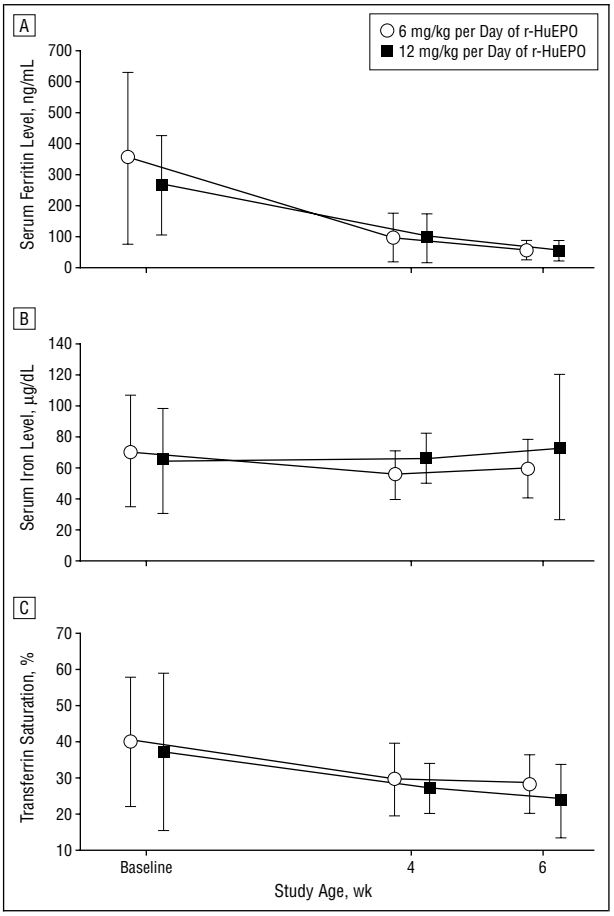

Figure 1. Ferritin levels (A), serum iron levels (B), and transferrin saturation (C) at baseline, 4 weeks, and 6 weeks of the study for the 6 mg/kg per day and 12 mg/kg per day iron supplementation groups. r-HuEPO indicates recombinant human erythropioetin.

The total reticulocyte count for both iron groups was significantly higher at 4 and 6 weeks of r-HuEPO therapy compared with baseline for each group ($P<.05$), even though there was no significant difference between the 2 iron supplementation groups (**Figure 2**).

Fourteen infants had either clinical or culture-proven sepsis during the study (11 in the 6 mg/kg per day iron group and 3 in the 12 mg/kg per day iron group). Clinical sepsis was defined as an infant developing clinical findings (temperature instability, lethargy, or poor perfusion) and laboratory value changes (leukocytosis, bandemia, neutropenia, or metabolic acidosis) that responded to antibiotic therapy. Eighteen episodes of sepsis were identified in the 14 infants. Four sepsis episodes were culture proven (3 in the 6 mg/kg per day iron group and 1 in the 12 mg/kg per day iron group) while 14 episodes were clinically diagnosed (11 in the 6 mg/kg per day iron group and 3 in the 12 mg/kg per day iron group). We did not see an increased incidence of sepsis episodes in the higher iron supplementation group.

COMMENT

We have shown that infants receiving 1200 IU/kg per week of r-HuEPO therapy decrease their iron stores while receiving 6 mg/kg per day or 12 mg/kg per day dose of

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supplemental enteral iron. There was no difference between the groups in the decrease of ferritin levels despite using a larger iron dose. No single laboratory test for evaluation of iron stores provides a complete picture. We compared the serum ferritin and serum iron level as well as the TIBC. Ferritin is considered the most specific indicator available to assess iron stores. Since we were using the high amount of iron, we wanted to be sure that this would not produce excess body iron. Our study shows that 12 mg/kg per day enteral iron did not produce gastrointestinal intolerance, and did not cause toxic levels of stored iron (high serum ferritin levels) or increase the incidence of sepsis.

In healthy infants, the serum ferritin level rises sharply in the first month of life when iron shifts from erythrocyte to the storage compartment[9,27-32] It then falls over the next 3 months as iron is used to meet the needs of the rapidly expanding erythrocyte mass. This may not be true for the premature infant in whom erythropoiesis may not start until later. Our study showed a marked variation in serum ferritin levels in both iron groups over the study, particularly at baseline. This variation in ferritin levels compounds the difficulty in interpreting whether an infant's iron stores are depleted and points out the need for studies that will establish normal values for ferritin in premature infants of different gestational age at different postconceptional age.

The decrease in ferritin levels and transferrin saturation in both the 6 mg/kg per day and 12 mg/kg per day iron groups may reflect iron use by augmented erythropoiesis.[32] However, we did not demonstrate a proportional increase in hematocrit in the 12 mg/kg per day iron group. Possible explanations for this include increased use of iron by other body tissues (eg, brain) or decreased absorption or retention of iron.[20-24] It has been suggested either that very low-birth-weight infants may poorly regulate iron absorption or that the level of serum ferritin is a poor marker of iron needs.[33,34]

It is possible that a decrease in enteral iron absorption could explain the lack of increase in the level of serum ferritin that we observed. Substances like phosphates and calcium may decrease iron absorption by forming insoluble complexes. Premature infants received high amounts of phosphorus and calcium in their premature formulas or were supplemented with calcium and phosphorus if receiving human milk. Additionally, we speculate that if more iron was used in the production of hemoglobin or that if iron was used for incorporation into other tissues, then the iron stores would not show an increase.

Our study used a higher dose of r-HuEPO (1200 IU/kg per week) than most other studies. This dose may have exacerbated the observed decrease in iron stores, despite iron supplementation as high as 12 mg/kg per day. An even higher dose of iron might improve the effectiveness of our higher dose r-HuEPO therapy. In a recent study, the effect on erythropoiesis was compared in very low-birth-weight infants with r-HuEPO treatment and receiving oral or parenteral iron. The infants receiving parenteral iron had significantly higher serum ferritin levels, but the hemoglobin and hematocrit values were not different between the 2 groups.[34] This lack of difference in hemoglobin and hematocrit suggests that despite a high serum ferritin level, the iron was unavailable for incorporation into the erythrocytes or that there was functional iron deficiency.

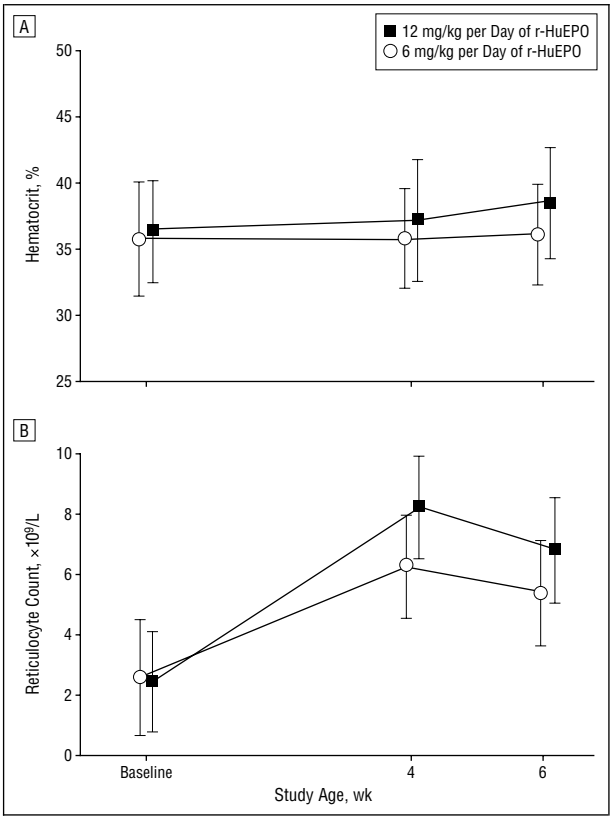

Figure 2. Hematocrit (A) and reticulocyte count (B) at baseline, 4 weeks, and 6 weeks of study for the 6 mg/kg per day and 12 mg/kg per day iron groups. r-HuEPO indicates recombinant human erythropioetin.

Parenteral iron use (but probably not enteral iron) carries a risk of iron overload.[35] The parenteral route bypasses the homeostatic control otherwise exerted through the gastrointestinal mucosa. Both iron dextran and iron sucrose, the available Food and Drug Administration–approved preparations of parenteral iron, form iron polymers that are absorbed intact into the lymphatic system. This may lead to serum iron levels that exceed the TIBC for several hours after the injection. This polymeric iron is not bound to transferrin and may encourage bacterial growth. In determining the appropriate dosage of supplemental iron, either high oral or parenteral, oxidative damage should be assessed. Free radical damage from iron excess may be more important to avoid than the intake of enough iron to produce erythropoiesis. Parenteral iron supplementation needs to be studied to prove its safety in premature infants before it is widely used.

We did not see an increase in sepsis in the 12 mg/kg oral iron group. Since there have been concerns that high iron supplementation may predispose to sepsis, this finding may be reassuring concerning the use of oral iron and the risk of infection.

We have shown that premature infants receiving 1200 IU/kg per week of r-HuEPO therapy decrease their iron stores while receiving 6 or 12 mg/kg per day of enteral iron supplementation. Considering the long-lasting and at times irreparable effects of iron deficiency

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What This Paper Adds

Adequate iron supply is essential for erythropoiesis in premature infants receiving high doses of r-HuEPO therapy. We hypothesized that using higher doses of r-HuEPO, which has been demonstrated to promote erythropoiesis, would require increased iron supplementation. We wanted to determine the dose of iron that would be sufficient to achieve maximal erythropoiesis without producing toxic effects. Therefore, we designed a prospective, randomized study to evaluate the effects of 2 different doses of enteral iron supplementation in premature infants who were receiving 1200 IU/kg per week of r-HuEPO therapy.

This study shows that following 4 and 6 weeks of r-HuEPO therapy with either 6 mg/kg per day or 12 mg/kg per day of oral iron supplementation, premature infants showed similar ferritin levels, serum iron levels, transferrin saturations, and hematocrits. Given that the ferritin levels were equal in the infants given twice as much iron as the lower-dose group, the additional iron was either poorly absorbed, not stored, or used by other tissues. We were unable to show better erythropoiesis in the infants with the high enteral iron dose. The optimal amount of iron, type of iron preparation, and route of administration for premature infants with augmented erythropoiesis remain to be determined.

during infancy,[36-40] iron supplementation needs to be sufficient to meet the iron demands of erythropoiesis as well as the needs of other tissues (eg, brain). The large variation in the level of serum ferritin and other measures of iron sufficiency make it difficult to determine the adequacy of iron stores. There are no sequential postnatal normal values of serum ferritin by gestational age. The optimal amount of iron, type of iron preparation, and route of administration for premature infants with augmented erythropoiesis remain to be determined.

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