

# Efficacy of erythropoietin in premature infants

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## ABSTRACT

**Objective:** To identify the effect of early parental recombinant human erythropoietin and iron administration on the blood transfusion requirement of premature infants.

**Methods:** In a controlled clinical trial conducted at the neonatal intensive care unit of Al-Hada Military Hospital, Taif, Kingdom of Saudi Arabia over a 16 months period, we assigned 20 very low birth weight infants with gestational age of (mean  $\pm$  standard error of mean)  $28.4 \pm 0.5$  weeks and birth weight of (mean  $\pm$  standard error of mean)  $1031 \pm 42$  gm, to receive either intravenous recombinant human erythropoietin 200 U/kg/day and iron 1mg/kg/day or conventional therapy over a 21 day study period. Blood transfusion administration undergoes a strict protocol in our nursery.

**Results:** During the 3 week study period, the hemoglobin and hematocrit remained similar in the 2 groups while the reticulocyte counts were greater in the recombinant human erythropoietin recipients on day 14. The number and volume of blood transfusions were similar in both groups.

**Conclusion:** Very low birth weight infants receive fewer blood transfusions than the number previously reported. Strict phlebotomy and transfusion criteria could minimize the need for human recombinant erythropoietin.

**Keywords:** Very low birth weight, human recombinant erythropoietin, total parenteral nutrition, intraventricular hemorrhage.

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Premature infants are at higher risks of developing a significant fall in hemoglobin and hematocrit value after birth.<sup>1,2</sup> This anemia of pre-maturity is a normocytic, normochromic anemia with low reticulocyte count, characterized by inappropriate low serum erythropoietin values.<sup>3,4</sup> Several factors may cause this type of anemia, such as blood loss, decreased erythrocyte life span, blood transfusions with adult hemoglobin, which favors tissue oxygenation and consequently a blunted hematopoietic stimulus and low serum erythropoietin levels.<sup>2,5,6</sup> Extremely low birth weight infants are the population at greater risk for repeated blood transfusion.<sup>7</sup> Recent studies suggest that treatment with recombinant human erythropoietin (r-HuEPO) can decrease the need for transfusion in premature neonates.<sup>7-9</sup> We believe that, management of this anemia may constitute a multifactorial approach

including minimizing blood sampling, decreasing donor exposure, and possibly treatment with r-HuEPO. Adverse reactions to blood transfusion in newborn are uncommon. Immune-mediated transfusion reactions are extremely rare in newborns, due to the immaturity of the immune system.<sup>10</sup> Decreasing donor exposure and the number of transfusion is an important strategy to decrease infectious exposure in this population of patients. Transmission of cytomegalovirus (CMV) is preventable with the use of leukocyte filters or CMV-negative products. However, transmission of human immunodeficiency virus (HIV) and hepatitis have devastating consequences in small numbers of infants.<sup>11</sup> Our implemented strategies for reducing blood transfusion in very low birth weight (VLBW) infants include the use of laboratory microtechniques and noninvasive monitoring to reduce blood loss as

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well as more conservative transfusion criteria and the possible benefits of r-HuEPO treatment for anemia of prematurity.

**Methods. Study design.** In a controlled clinical trial of VLBW infants (mean birth weight of  $1031 \pm 42$  gm), we assigned 2 groups of infants. The first group received r-HuEPO and iron intravenously and the 2nd group had conventional therapy, blood transfusion without r-HuEPO. Infants were eligible for study if they weighed 1250 grams or less at birth and less than 7 days of age. Infants were not eligible for study if they have hemolytic or hemorrhagic disease, if they have neutropenia (absolute neutrophil count less than 500 cells/MC), if they have evidence of seizures or hypertension, mean blood pressure exceeding the 95th percentile for gestational age.

**Treatment.** Infants in the recipients group, received 200 u/kg/day r-HuEPO intravenously over 4 hours for 14 consecutive days. The r-HuEPO was diluted in 2ml of 5% albumin; they received 1mg/kg/iron dextran (iron hydroxide saccharate) in their total parenteral nutrition (TPN) solution, during the 14-days treatment period.

**Transfusion therapy.** Our standard criteria for blood transfusions for both groups were: for infants requiring mechanical ventilation, transfusion was given if the hematocrit fell below 33ml/dl (33%). For infants not receiving mechanical ventilation, transfusions were given if the hematocrit fell below 28ml/dl (28%) and the infant was experiencing symptoms. Transfusion consisted of 15 ml/kg of packed erythrocytes reconstituted to a hematocrit of 75ml/dl over 4 hours.

**Clinical monitoring.** Symptoms of anemia were defined as tachycardia (heart rate  $> 160$  beats/min, as the average of all heart rates over a 24-hour period), an increased oxygen requirement (as increase in fraction of inspired oxygen of  $> 0.20$  over 24-hour period). Heart rate, respiratory rate, blood pressure, and transfusion reactions were monitored during the treatment period.

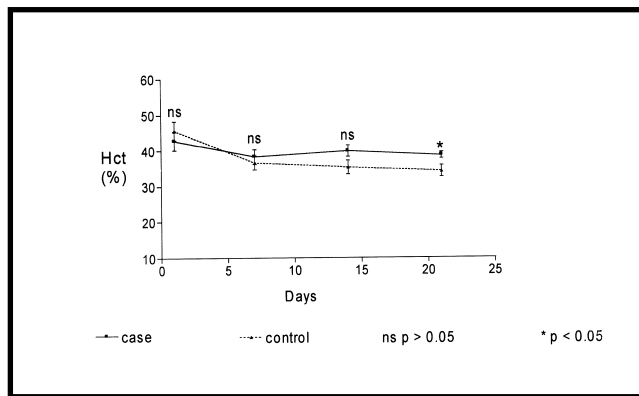
**Statistical methods.** Power analysis using Graph Pad StatMate version 1.00, 1995, (with a 2-sided significance level of 0.05 and a power of 80%) required that 10 patients were needed in each group to have 80% probability of detecting a difference of 20ml transfused blood to 1kg/patient or more. Data were analyzed using Statistical Package for Social Sciences (SPSS) software (version 10) with significance level of  $P > 0.05$  accepted as being statistically significant. The unpaired T-test and Fisher exact tests were used to compare continuous variables and categorical variables, for example sex, patent ductus arteriosus and number of ventilated infants.

**Results.** Ten infants were eligible for the study and 10 infants were assigned as controls. There was no differences between groups in birth weight, gestational age or birth hematocrit at study entry. Characteristics of 10 r-HuEPO recipients and the 10 controls are shown in (Table 1). There was no death in both groups and no infant was withdrawn from the study. Hematocrit and hemoglobin were declined on day 7 and 14 in both groups but were lower in the control group, however, not significant statistically (Figure 1 & 2). Absolute reticulocyte counts declined on day 7 but increased dramatically on day 14, remained elevated by day 21 in the r-HuEPO group and slightly elevated in the control group (Figure 3). Phlebotomy losses were similar in the 2 groups ( $33.5 \pm 3.3$  ml/kg r-HuEPO recipients and  $31.5 \pm 5.1$  ml/kg control,  $p=0.747$ ), and there were no significant differences in the number and volume of transfusion per patient. Erythropoietin (EPO) recipients averaged  $1.81 \pm 0.69$  transfusions and  $27.2 \pm 10.4$  ml/kg packed erythrocytes during the 21-day study period, whereas the control group averaged  $1.86 \pm 0.67$  transfusions and  $27.9 \pm 10.1$  ml/kg packed erythrocytes ( $p=0.962$ ). There were no adverse effects of r-HuEPO or parental iron administration noted.

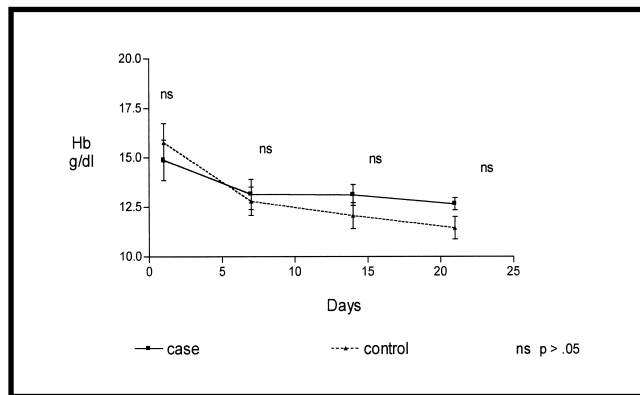
**Discussion.** Initial studies utilizing an adult dose of r-HuEPO reported little or no effect.<sup>12</sup> Pharmacokinetic studies in newborn monkeys and sheep indicated that neonates have a larger volume of

Table 1 - Characteristics of the study infants.

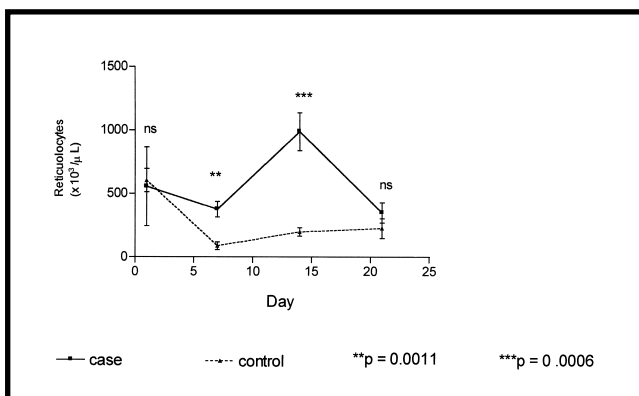
Item	EPO group (N=10)	Conventional group (N=10)	*P Value
Birth weight (gm)	$1002 \pm 42.37$	$1061.5 \pm 41.96$	0.332
Gestation (wk)	$28.4 \pm 0.52$	$28.6 \pm 0.48$	0.780
Age (hr)	$31.2 \pm 7.2$	$24 \pm 0$	0.343
Hematocrit (%)	$42.76 \pm 2.63$	$45.62 \pm 2.7$	0.458
Male/female	4/6	4/6	1.00
Number ventilated	8 (80%)	8 (80%)	1.00
PDA	4 (40%)	2 (20%)	0.628
Hemoglobin level (gm/dl)	$14.88 \pm 1.03$	$15.77 \pm 0.96$	0.536
Absolute reticulocyte count ( $\times 10^9/L$ )	$554.56 \pm 308.78$	$603.8 \pm 91.53$	0.886
N - number, EPO - erythropoietin, gm - grams, wk - week, hr - hour, PDA - patent ductus arteriosus, *values represent mean $\pm$ standard error of mean			



**Figure 1** - Changes in hematocrit (Hct) percentages for cases and controls during the study (values represent mean  $\pm$  standard error of mean).



**Figure 2** - Changes in hemoglobin (Hb) percentage for cases and control during the study (values represent mean  $\pm$  standard error of mean).



**Figure 3** - Changes in reticulocyte count for cases and controls during the study (values represent mean  $\pm$  standard error of mean).

distribution and more rapid elimination of r-HuEPO,<sup>13</sup> necessitating the use of higher doses than required for adults. These differences were found to apply to pre-term infants as well.<sup>14</sup> Ohls et al reported in VLBW infants, administration of r-HuEPO and parental iron in the first 2 weeks of life was associated with decrease in the number and volume of transfusion received.<sup>7</sup> Investigators have shown that smaller, sicker infants at increased risk for transfusion might benefit from r-HuEPO therapy, while other studies in adults and pediatric patients have reported limited erythropoiesis when iron supplementation is adequate.<sup>12, 13</sup> Ohls et al, also noted that (VLBW) infants who did not receive r-HuEPO treatment, had more than a 50% reduction in transfusion requirements, compared with infants not enrolled in the study.<sup>14</sup> The European Multicentre Erythropoietin Study Group observed 1.39 total transfusions per patient of healthy infants. Shanon et al,<sup>15</sup> reported a mean of 5.3 transfusions in infants with birth weight less than 1250gm who were healthy and able to tolerate oral iron and vitamin E treatment. Moreover, Asch et al<sup>16</sup> reported a limited role of EPO treatment in the care of VLBW babies and it is not cost-effective for the prevention of anemia of prematurity. In the present study we noticed that, parenteral administration of r-HuEPO and iron has a significant effect on the hemoglobin and hematocrit level of the recipient, but it was not associated with decrease in number or volume of blood transfusion or with any side effects. These results, could be explained by many factors, such as, allowing some greater degree of anemia in these infants before blood transfusion, our strict blood sampling protocol by using pulse oximetry, transcutaneous blood gases monitoring and reducing the frequency of blood sampling during parenteral nutrition. The lower numbers of blood transfusions can be attributed to the higher baseline hematocrit of (44.19% $\pm$ 2.65) and the relative stable conditions of the studied infants. While it is known that treatment with r-HuEPO can increase the number of reticulocytes and the hemotocrit and decrease the number of transfusions, the justification for routine use for anemia of prematurity is yet to be determined.

In conclusion, although r-HuEPO has been shown to be effective in treatment of anemia of prematurity in larger, stable neonates. Our data indicates that routine r-HuEPO treatment of VLBW infants has a very limited role in minimizing blood transfusion requirement of those patients and is not cost-effective. Phlebotomy practices and blood banking techniques have to be modified to meet the needs of VLBW infants.

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