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Erythropoietin increases reticulocyte counts and maintains hematocrit in neonates requiring surgery*

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Abstract

Background—Limited erythropoietin (Epo) production diminishes neonates' ability to regenerate blood removed by phlebotomy. Neonates requiring surgery are at risk to receive multiple transfusions. We sought to determine if recombinant Epo administration to neonates requiring surgery would stimulate erythropoiesis.

Methods—Infants were randomized in double-masked fashion to receive Epo (200 units kg⁻¹ d⁻¹) or placebo for 14 days. Complete blood count, absolute reticulocyte count (ARC), phlebotomy losses, and transfusions were measured during the study period. Infants were transfused using a strict transfusion protocol.

Results—In the Epo group (n = 10, 2034 ± 308 g, 8 ± 2 days old; mean ± SEM), ARC increased significantly, whereas in the placebo group (n = 10, 2400 ± 184 g, 7 ± 2 days old), ARC remained low. Hematocrits in the Epo group trended upward from 34.4 ± 1.7% to 37.3 ± 1.9% (although not statistically significant) despite phlebotomy losses of 53 ± 12 mL/kg. Hematocrits in the placebo group were 35.9 ± 1.8% and 33.2 ± 1.6% on days 1 and 15, respectively, with phlebotomy losses of 27 ± 5 mL/kg. There were no differences in absolute neutrophil counts or platelet counts between groups at the end of the study. No adverse effects were noted.

Conclusions—Infants randomized to Epo increased reticulocyte counts and hematocrits without adverse effects. Erythropoietin administration may provide an adjunct to present care in decreasing or eliminating erythrocyte transfusions in surgical neonates.

Keywords

Erythropoietin; Transfusions; Neonate; Erythropoiesis; Mitogen

1. Background

Human recombinant erythropoietin (Epo) administration to preterm infants decreased transfusions to varying degrees in clinical studies [1–3]. Neonates who are born with problems that require surgical repair such as omphalocele, gastroschisis, meningomyelocele, congenital diaphragmatic hernia, or craniofacial abnormalities often undergo surgery during the period of physiologic anemia. These infants are hospitalized and undergo blood loss through phlebotomy, surgical blood loss, and postoperative care. As a result, their physiologic anemia is exacerbated, and hemoglobin concentrations may drop to such a low level that packed red blood cell (PRBC) transfusions are given. These transfusions result in

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significantly decreased endogenous erythropoiesis [4]. Moreover, guidelines for transfusion have been slow to develop in these neonates because of the appearance of a lack of reserve or tolerance to lower hematocrits. Recent studies in ill, preterm infants, children, and adults have proven that more restrictive transfusion criteria can be used without compromising patient outcome or hospital stay and may in fact improve outcomes [1–3,5–7].

As part of blood conservation efforts in adults, Epo is safe and effective when administered before elective surgery [8–11]. Studies have been performed in the pediatric surgical population [12–20]; however, the total number of neonates evaluated is minimal. Based on previous studies in preterm neonates, it seemed reasonable to extend the use of Epo to other neonatal populations where the risk of multiple transfusions exist. The purpose of this randomized, masked, placebo-controlled study was to determine if Epo could be used safely and efficaciously in neonates requiring major surgery. We hypothesized that short-term Epo administration would stimulate erythropoiesis, reflected by increased reticulocyte counts.

2. Methods

Infants were eligible for study if they had a diagnosis of a disease requiring major surgery (defined as surgery requiring at least 15 minutes of general anesthesia or surgery where anticipated blood loss was 10 mL/kg body weight or greater), if they were less than 28 days old at the time of study entry, and if informed consent was obtained. Infants were ineligible for study if it was deemed unlikely that they would survive more than 72 hours, if they required extracorporeal membrane oxygenation, if they had Coombs-positive hemolytic disease, if they had evidence of disseminated intravascular coagulation, if clinical seizures were present, if they had systolic blood pressures greater than 100 mm Hg (while not on pressor support) during the first 96 hours after birth, if their hematocrit was greater than 50%, or if they were receiving Epo clinically.

Infants were randomized to Epo or placebo groups by a random number list and were stratified by weight (≥ 1500 and < 1500 g). Epo or placebo was dispensed from the pharmacy in total parenteral nutrition (TPN) for intravenous (IV) administration or in syringes for subcutaneous (SC) dosing. Infants randomized to Epo received a dose of 200 units $\text{kg}^{-1} \text{d}^{-1}$ added to their TPN solution [21] or 400 units/kg SC 3 times weekly. The dose was initially based on study entry weight and adjusted weekly for changes in weight. If IV access was not present, Epo was administered SC. For infants randomized to receive placebo, IV administration consisted of TPN with placebo (an equal volume of normal saline) added, whereas SC administration consisted of sham dosing, followed by placement of a BandAid over the sham injection site. Dosing continued until the infant reached study day 14 unless the infant was discharged from the hospital or died before the end of the study period.

Each study subject had a complete blood count with reticulocyte count performed on the 1st (drawn prior to study drug administration), 8th, and 15th day of study. Absolute reticulocyte counts (ARCs) were calculated by multiplying the red blood cell count by the percent reticulocytes seen on peripheral smear and reported as number of cells $\times 10^3/\mu\text{L}$. All available laboratory information was recorded on each patient (eg, hemoglobin from blood gas measurements, additional complete blood counts, etc). All phlebotomy losses, transfusions, and transfusion volumes were recorded.

During the study period, a strict transfusion protocol (Table 1) was used to administer PRBC transfusions [2]. Infants were not transfused to replace blood lost through phlebotomy. Infants received oral iron supplementation when enteral feeds reached 60 mL $\text{kg}^{-1} \text{d}^{-1}$.

Data were analyzed using a commercial data analysis program (StatView, Abacus Concepts, Inc, Berkeley, CA). Differences in hematocrit, ARC, phlebotomy losses, and number of

transfusions were compared using paired and unpaired *t* tests. Data that were not parametrically distributed were analyzed using the Wilcoxon signed rank test. In our previous studies in preterm infants, we found a difference in reticulocyte counts of $150 \pm 70 \times 10^3/\mu\text{L}$ during a 2- to 4-week period between the treated and placebo groups [1,2]. Based on those studies, 10 infants in each group were required to obtain an α of .05 with 90% power (estimating a dropout rate of 30%).

3. Results

From August 2001 to May 2005, 122 pediatric surgical neonates were evaluated for possible entry into the study. A total of 61 infants met study criteria, and 20 infants were enrolled and completed the study protocol, 10 in each of the placebo and Epo groups. Parents of 30 eligible infants refused the study, 6 infants were enrolled in a competing study, and the parents of 5 infants could not be contacted for consent within the study period. All data on enrolled infants are presented.

Infant characteristics (birth weight, gestational age, age upon entry into study, hematocrit, and ARC) were similar between the 2 groups at baseline (Table 2; all values mean $\pm$ SE). Infants had similar indications for surgery between the 2 groups. In the Epo group, there were 3 infants with gastroschisis, 3 infants with necrotizing enterocolitis (NEC) requiring surgical exploration, 2 infants with congenital diaphragmatic hernia, and 2 infants with intestinal atresia. In the placebo group, there were 5 infants with gastroschisis, 2 infants with intestinal atresia, 1 infant with NEC requiring surgical exploration, 1 infant with congenital diaphragmatic hernia, and 1 infant with tracheoesophageal fistula.

Absolute reticulocyte count in the Epo group increased significantly during the study period, whereas ARC in the placebo group did not (Fig. 1). Absolute reticulocyte count was significantly higher in the Epo vs placebo groups on day 8 ($P = .048$) and day 15 ($P = .008$) as well as within the Epo group day 1 vs day 15 ($P = .03$).

Hematocrit in the Epo group increased from $34\% \pm 2\%$ to $37\% \pm 2\%$ (Fig. 2), although this difference did not reach statistical significance. Hematocrit in the placebo group was $36\% \pm 2\%$ at baseline and $33\% \pm 2\%$ at the end of the study. There were no differences between groups in hematocrit during the 2-week study period. Although absolute neutrophil counts were statistically higher at the start of the study in the Epo group compared to the placebo group ($P = .017$), there were no statistical differences in absolute neutrophil counts or platelet counts between groups at the end of the study.

Infants in the Epo group, although not by design, were the sicker population, requiring more frequent laboratory evaluation and a greater number and volume of transfusions (Table 3). Phlebotomy losses trended higher in the Epo group (19 ± 12 mL/kg) during the study but were not statistically higher than the placebo group (11 ± 3 mL/kg; $P = .103$). Phlebotomy losses during hospitalization were nearly twice as large in the Epo group as the placebo group, 53 ± 12 vs 26 ± 5 mL/kg ($P = .065$ Epo vs placebo). A total of 9 transfusions were administered during the 2-week study period, for an average of 0.8 transfusion per patient in the Epo group and 0.1 transfusion in the placebo group ($P = .07$). In all, infants received 1.3 ± 0.7 transfusions and 30 ± 9 mL/kg in PRBC transfusion volume during the course of their hospitalization.

4. Discussion

Neonates requiring surgery for congenital anomalies often require PRBC transfusions and might benefit from an erythropoiesis stimulating agent. We found that administering Epo to these neonates significantly increased reticulocyte counts and maintained hematocrit, despite

phlebotomy losses that trended higher than that recorded in the placebo group. Reticulocyte counts in the Epo group increased throughout the study period, whereas those in the placebo group showed a steady decline. This decline did not appear to be because of lack of response to Epo itself, but rather because of the inability of the infant to increase endogenous Epo production in response to phlebotomy loss [4]. The Epo-induced erythropoiesis maintained the hematocrit in treated infants despite significant phlebotomy losses. The study was not designed to show a difference in number of transfusions, and in fact, transfusions in the Epo group were greater throughout hospitalization because of the more critical nature of their illness. In particular, 3 infants in the Epo group had prolonged courses of NEC and required a total of 4, 4, and 8 PRBC transfusions, respectively. To test for differences in transfusions, a longer administration period would be required.

In term infants, the fall in red cell production after birth is the result of improved oxygenation and a natural adaptation to extrauterine life. The hemoglobin concentration decreases over the first 2 to 3 months of life, remains stable over the next several weeks, then slowly rises in the fourth to sixth month of life in response to increased Epo concentrations [22,23]. The decrease in hemoglobin concentration has thus been termed a “physiologic nadir,” rather than true anemia. The drop in hematocrit during the transition from a relative hypoxic in utero environment to an oxygen enriched ex utero environment is well tolerated by healthy newborns. It is not known whether sick, surgical neonates would tolerate a similar or exaggerated drop in hematocrit because most of these neonates are transfused at a higher hematocrit.

The use of Epo to facilitate autologous blood donation has been studied extensively in the adult population, and recommendations by the Society of Thoracic Surgeons Blood Conservation Guidelines Taskforce have published recommendations for the use of Epo as part of a comprehensive approach to blood conservation [11]. Recommendations have not been published for the pediatric population. Studies have evaluated Epo administered to children requiring a variety of major surgical procedures, including open heart surgery, craniostomy repair, and corrective spinal surgery [12–20]. In studies of older pediatric patients, autologous blood was collected after children received Epo therapy preoperatively and was used during surgery for blood loss [13–16]. In children undergoing cardiac surgery, Sonzogni et al [15] reported a decrease in requirement of allogeneic transfusion from 61.5% in the group that did not receive Epo to 7.7% in children given Epo, all of which had received the full volume of blood donated autologously in the preoperative period. In children undergoing spinal surgery, Franchini et al [16] reported a significant decrease in the need for allogeneic blood transfusion in the Epo-treated group compared to the control group.

Studies have shown that Epo can reduce the transfusion requirements for infants undergoing craniofacial surgery [13,18,20]. Meneghini et al [18] reported a decreased number of homologous PRBC transfusions in infants pretreated with Epo who underwent normovolemic hemodilution before surgery, compared to historical controls. Krajewski et al [20] increased hematocrit and decreased transfusion requirements in infants treated preoperatively with Epo who underwent surgery using cell saver techniques.

Because of challenges in preoperative autologous blood donation in younger pediatric populations, investigators evaluated single or multiple doses of Epo to stimulate erythropoiesis in infants and children before cardiac surgery [12,19]. Shaddy et al [12] administered Epo to infants awaiting heart surgery and reported a significant increase in hematocrit and reticulocyte count. Ootaki et al [19] administered a single preoperative dose of Epo before cardiac surgery to 82 children. Although there was not a significant reduction in transfusions, the single dose was found increase hematocrit levels.

Other possible benefits of Epo administration exist for critically ill infants requiring surgery. Epo appears to have a trophic effect on early development of gastrointestinal tract vasculature and may be an endogenous stimulant of vessel growth [24]. It has also been shown in animal models to restore villus damage and improve peristalsis associated with gastroschisis [25]. Neuroprotective effects are a possible additional benefit of Epo administered to neonates, in that neurodevelopmental outcomes are improved in extremely low birth weight (ELBW) infants receiving Epo with increased serum Epo concentrations [26]. Studies are in process evaluating this potential benefit in term and preterm infants [27,28].

The application of restrictive transfusion guidelines has decreased the use of red cell transfusions significantly in critically ill adults, children, and neonates; however, restrictive transfusion guidelines have been slow to be adopted in pediatric surgical populations. Although significant acute blood loss is a common rationale for administering red cell transfusions, further thoughtful study is required to determine risks vs benefits of this therapy and to determine if, similar to previously studied critically ill patients, a more restrictive approach to red cell transfusions could be applied to this population [29].

This pilot study was designed to determine if further investigation of Epo administration is warranted in this population, especially with respect to reducing transfusion requirements. It is limited in the number of infants enrolled, in the size of the infants studied, and in the restricted time course of Epo treatment. We speculate that the significant increase in reticulocyte counts seen in our study might also occur when Epo is administered over a longer period in a larger study population, possibly leading to increased or stabilized hematocrit and decreased transfusion requirements. Our results extend the utility of Epo to increase reticulocyte counts and maintain hematocrit in neonates requiring a broad spectrum of surgical intervention.

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Fig. 1.

Absolute reticulocyte counts (ARC) in neonates receiving Epo (grey columns) or placebo (white columns) during the 2-week study period. Values are shown as mean $\pm$ SE. ARC was significantly increased from day 1 to day 8 and 15 in the EPO group, but did not increase in the placebo group. * $P < .05$, EPO versus placebo day 8 and day 15; ‡ $P < .05$, Epo at day 8 and 15 versus baseline.

Fig. 2. Hematocrit (Hct) in neonates receiving Epo (grey columns) or placebo (white columns) during the 2-week study period. Values are shown as mean $\pm$ SE. There was no statistical difference between study groups in Hct and no statistical change in Hct occurred during the 2-week study period.

Table 1**Transfusion criteria**

Infants requiring moderate or significant mechanical ventilation, defined as MAP >8 cm H ₂ O and Fio ₂ >0.40	Hematocrit ≥35%, hemoglobin ≥11 g/dL
Infants requiring minimal mechanical ventilation, defined as MAP ≥8 cm H ₂ O and/or Fio ₂ ≥0.40	Hematocrit ≥30%, hemoglobin ≥10 g/dL
For infants on supplemental oxygen who are not requiring mechanical ventilation, and 1 or more of the following is present: <ul style="list-style-type: none"> • ≥24 h of tachycardia (heart rate >180) • ≥24 h of tachypnea (RR >80) • An increased oxygen requirement from the previous 48 h, defined as ≥4-fold increase in nasal canula flow (ie, 1/4–1 L/min) or an increase in nasal continuous positive airway pressure ≥20% from the previous 48 h (ie, 10–12 cm H₂O) • Lactate ≥2.5 mEq/L • Weight gain <10 g kg⁻¹ d⁻¹ over the previous 4 d while receiving ≥100 kcal kg⁻¹ d⁻¹ • Multiple episodes of apnea and bradycardia (≥10 episodes in a 24-h period or ≥2 episodes in a 24-h period requiring bag-mask ventilation) while receiving therapeutic doses of methylxanthines • Undergoing major surgery within 72 hours 	Hematocrit ≥25%, hemoglobin ≥8 g/dL
Infants on room air without any symptoms and the ARC is <100,000 cells/3L	Hematocrit ≥20%, hemoglobin <7 g/dL

MAP indicates mean airway pressure; RR, respiratory rate.

Table 2

Infant characteristics

	Epo (n = 10)	Placebo (n = 10)
Birth weight (g)	2034 ± 308	2400 ± 184
Gestation at birth (wk)	34.1 ± 1.7	36.6 ± 0.7
Age (d)	8 ± 2	7 ± 2
Hematocrit (%)	34.4 ± 1.7	35.9 ± 1.8
ARC ($\times 10^3/\mu\text{L}$)	94 ± 13	88 ± 20
Platelet Count ($\times 10^3/\mu\text{L}$)	273 ± 43	210 ± 29
Absolute neutrophil count ($\times 10^6/\mu\text{L}$)	10.3 ± 1.8 *	5.0 ± 0.8

* $P < .05$, Epo vs placebo.

Table 3

Phlebotomy and transfusions

	Epo (n = 10)	Placebo (n = 10)
Phlebotomy during study (mL/kg)	19 ± 4	11 ± 3
Phlebotomy during hospitalization (mL/kg)	53 ± 12	27 ± 5
Transfusions during study (#/pt)	0.8 ± 0.3	0.1 ± 0.4
Transfusions during hospitalization (#/pt)	2.1 ± 0.5	0.5 ± 0.2
Volume transfused during study (mL/kg)	17 ± 4	4 ± 4
Volume transfused during hospitalization (mL/kg)	43 ± 15	16 ± 7
Donor exposure during hospitalization (#/pt)	1.1 ± 0.4	0.4 ± 0.2

pt indicates patient.