A Randomized, Masked Study of Weekly Erythropoietin Dosing in Preterm Infants

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Objective To compare reticulocyte responses of once-per-week erythropoietin (EPO) dosing with 3-times-a-week dosing in preterm infants.

Study design Infants weighing ≤1500 g and ≥7 days of age were randomized to once-per-week EPO, 1200 U/kg/dose, or 3-times-a-week EPO, 400 U/kg/dose, subcutaneously for 4 weeks, along with iron and vitamin supplementation. Complete blood counts, absolute reticulocyte counts (ARCs), transfusions, phlebotomy losses, and adverse events were recorded.

Results Twenty preterm infants (962 ± 55 g, 27.9 ± 0.4 weeks, 17 ± 3 days of age) were enrolled. Groups were similar at baseline. Infants in both groups had increased ARCs, which were similar between treatment groups at the start and end of 4 weeks. Hematocrit remained stable, and similar numbers of transfusions were administered. No adverse effects of either dosing schedule were noted.

Conclusions Preterm infants respond to weekly EPO by increasing ARCs and maintaining hematocrit. We speculate that once-per-week EPO dosing might be beneficial to preterm infants requiring increased erythropoiesis. *(J Pediatr 2012;160:790-5)*.

Erythropoietin (EPO) effectively increases and maintains hematocrit (Hct) using once-per-week dosing in adults with anemia due to end-stage renal disease and in adults with cancer. Dosing schedules in adults have progressed from 3-times-per-week dosing 2 decades ago to once-per-week dosing currently.[1,2] EPO has been used in preterm infants to prevent and treat the anemia of prematurity and is usually given 3-times-per-week as a subcutaneous (SC) injection.[3] Alternatively, EPO can also be given intravenously by adding it daily to parenteral nutrition solution.[4] Although the pharmacokinetics of EPO in preterm infants would suggest the desirability of more frequent dosing,[4-6] the *erythrokinetics* of EPO—the response of red cell precursors to EPO—may allow for less frequent dosing. In addition, recent studies evaluating nonhematopoietic, neuroprotective effects of EPO have used higher doses to achieve higher serum and presumably cerebrospinal fluid concentrations.[7,8] Once-per-week dosing of EPO might also achieve increased serum concentrations, thus potentially providing neuroprotection in addition to erythropoietic stimulus. We investigated whether weekly EPO would result in a similar reticulocyte response to 3-times-per-week dosing in preterm infants.

Methods

Infants were eligible for study if they met the following entry criteria: birth weight ≤1500 grams, gestational age ≤32 weeks, Hct ≤48%, ≥7 days of age, and informed consent was obtained from a parent or guardian. Infants were ineligible for study if they were already receiving EPO or were enrolled in an EPO study, if they were not expected to survive, if they had Coombs-positive hemolytic disease, if clinical seizures were present, if they had known thromboses, if they had a major congenital malformation (such as trisomy 21, 18, or 13 or complex cyanotic congenital heart disease), or if they had systolic blood pressures >100 mm Hg while not on pressor support. The study was approved by the Human Research Review Committee at the University of New Mexico.

Infants were randomized using a random number table generated by a statistical program (SysStat Software, Inc, Chicago, Illinois) to 1 of 2 treatment groups: EPO (Amgen, Thousand Oaks, California) 1200 U/kg once per week SC or EPO 400 U/kg/dose 3 times per week SC (our current clinical dosing schedule). All providers aside from the research nurse were masked to the treatment group. Infants in the once-per-week dosing group received sham SC injections for the other 2 dosing periods each week. An adhesive bandage covered the true and sham injection sites. The study

ARC	Absolute reticulocyte count
CEV	Circulating erythrocyte volume
EPO	Erythropoietin
Hct	Hematocrit
IVH	Intraventricular hemorrhage
NICU	Newborn intensive care unit
ROP	Retinopathy of prematurity
SC	Subcutaneously
TPN	Total parenteral nutrition

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drug was brought to the bedside in a closed container, and injections were shielded from the caregivers by screens. Twins were randomized to the same treatment group.

EPO was dispensed from the pharmacy in 29½ gauge, 0.3-mL syringes for SC dosing. Infants weighing ≤1000 g at any time during the study received the following dose: using a concentration of 2000 U/mL, the 3-times-per-week dosing volume was 0.2 mL/kg body weight. Using a concentration of 4000 U/mL, the once-per-week dosing volume was 0.3 mL/kg body weight. Infants weighing >1000 g at any time during the study received the following dose: using a concentration of 4000 U/mL, the 3-times-per-week dosing volume was 0.1 mL/kg body weight. Using a concentration of 10 000 U/mL, the once-per-week dosing volume was 0.12 mL/kg body weight. The rationale for using different concentrations of EPO was to maintain the total dosing volume between 0.1 mL and 0.3 mL. The administration of a dose <0.1 mL is technically difficult, and a dose >0.3 mL in a small infant increases discomfort. The dose was initially based on study entry weight, and was adjusted weekly for changes in weight. The dosing continued until the infant reached study day 28, was discharged from the hospital, or was transferred to another hospital. Only the research pharmacist and the research nurse giving the SC injection knew what the infant was receiving.

All infants received 6 mg/kg/day elemental iron while receiving ≥60 mL/kg/day of enteral feedings. For infants who received <60 mL/kg/day enteral feeds and had total parenteral nutrition (TPN) ordered, parenteral iron in the form of iron dextran was administered once a week in the TPN. A baseline ferritin was measured, and parenteral iron dosing was based on the results (dosing was determined by the research nurse).[3] For infants with a baseline ferritin between 100 and 400 ng/mL, parenteral iron dosing was given at a dose of 3 mg/kg once per week in TPN, for up to 2 doses. For infants with a baseline ferritin <100, a third parenteral iron dose was given if the infant was still on TPN. For infants with a baseline ferritin >400, no parenteral iron was given. All infants on any enteral feeds received 15 IU of oral vitamin E each day and 50 μg of oral folate each day.

Each infant had a complete blood count with differential and reticulocyte count performed at baseline (drawn prior to study drug) and day 14 and day 28 of study (labs were not redrawn if sufficient blood could not be obtained or if the sample clotted). Absolute reticulocyte counts (ARCs) were determined based on the percent reticulocyte count × red blood cell count (10^6 cells/mL). Circulating erythrocyte volume (CEV; mL) was calculated based on an estimated blood volume of 85 mL/kg, the weight of the infant on the day the complete blood count with differential was drawn, and the Hct, in order to evaluate the effect of EPO on erythropoiesis. In addition, each subject had a serum ferritin measured at the beginning and end of study. During the study, the standard newborn intensive care unit (NICU) transfusion protocol implemented in 2004 at the University of New Mexico was used to administer packed red blood cell transfusions (Table I; available at www.jpeds.com). Transfusions were considered (but not mandated) when infants reached the Hct levels listed.

Data Analysis and Power Analysis

Statistical analyses were performed using R.[9] Differences in Hct, reticulocyte count, and transfusion number and volumes were compared using paired and unpaired *t* tests or ANOVA. The primary outcome variable was change in reticulocyte count from baseline. Previous studies in preterm infants receiving EPO (compared with placebo) have shown a difference in reticulocyte counts of $150 \pm 70 \times 10^3$ cells/μL during a 2- to 4-week period.[3] We previously evaluated 2 dosing schedules and reported a difference in reticulocyte response of 75×10^3 cells/μL.[4] Based on a difference in the means of 75×10^3 cells/μL and a SD of 50×10^3 cells/μL, a total of 8 infants in each group were required to obtain an α of .05 with 80% power. As this was a pilot study, we did not determine a sample size based on equivalence between the 2 dosing schedules. An equivalence study would require 223 infants in each arm to determine if the 2 dosing schedules were similar, using an equivalence interval for mean differences of $\pm 25 \times 10^3$ cells/μL and observed an SD of approximately 90 $\times 10^3$ cells/μL for differences between baseline and endpoint values. We planned to enroll 10 infants in each group to allow for patient dropout.

Results

Twenty preterm infants (10 in each treatment group; 1 set of twins in the once-per-week treatment group) were enrolled at the University of New Mexico between April 2006 and March 2009. One infant in each of the treatment groups died from necrotizing enterocolitis. Infant characteristics (birth weight, gestational age, age upon entry into study when first dose of study drug was administered, hematologic variables) were similar between the 2 groups at baseline (Table II). Four of 10 infants in each group were still receiving TPN. All surviving infants were fed breast milk plus fortifier (6 of 9 in each group) or premature formula, enriched to 24-26 calories per ounce.

ARCs (Figure 1) increased during the study period (NS for baseline versus week 2 in both groups; NS for baseline versus week 4 in once-per-week group; $P < .01$, baseline versus week 4 in the 3-times-per-week group). ARCs were similar between groups at baseline and 2 weeks and 4 weeks of the study. Because of a lack of data points due to insufficient blood samples, the difference between baseline ARCs and ARCs at 4 weeks was NS in the once-per-week EPO group.

There were no significant differences between groups in Hct during the 4-week study period, and no significant differences within groups over the 4 weeks of study (Figure 2). CEVs were calculated by multiplying study Hct with an estimated blood volume of 85 mL/kg and an estimated weight increase of 2% per day. CEV in both treatment groups increased significantly from baseline over the 4-week study period (Figure 3).

There were no statistical differences in absolute neutrophil counts between groups throughout the study. For all subjects,

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