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Randomized Trial of Liberal Versus Restrictive Guidelines for Red Blood Cell Transfusion in Preterm Infants

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Abstract

Objective—Although many centers have introduced more restrictive transfusion policies for preterm infants in recent years, the benefits and adverse consequences of allowing lower hematocrit levels have not been systematically evaluated. The objective of this study was to determine if restrictive guidelines for red blood cell (RBC) transfusions for preterm infants can reduce the number of transfusions without adverse consequences.

Design, Setting, and Patients—We enrolled 100 hospitalized preterm infants with birth weights of 500 to 1300 g into a randomized clinical trial comparing 2 levels of hematocrit threshold for RBC transfusion.

Intervention—The infants were assigned randomly to either the liberal- or the restrictive-transfusion group. For each group, transfusions were given only when the hematocrit level fell below the assigned value. In each group, the transfusion threshold levels decreased with improving clinical status.

Main Outcome Measures—We recorded the number of transfusions, the number of donor exposures, and various clinical and physiologic outcomes.

Results—Infants in the liberal-transfusion group received more RBC transfusions (5.2 ± 4.5 [mean ± SD] vs 3.3 ± 2.9 in the restrictive-transfusion group). However, the number of donors to whom the infants were exposed was not significantly different (2.8 ± 2.5 vs 2.2 ± 2.0).

There was no difference between the groups in the percentage of infants who avoided transfusions altogether (12% in the liberal-transfusion group versus 10% in the restrictive-transfusion group). Infants in the restrictive-transfusion group were more likely to have intraparenchymal brain hemorrhage or periventricular leukomalacia, and they had more frequent episodes of apnea, including both mild and severe episodes.

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No conflict of interest declared.

Conclusions—Although both transfusion programs were well tolerated, our finding of more frequent major adverse neurologic events in the restrictive RBC-transfusion group suggests that the practice of restrictive transfusions may be harmful to preterm infants.

Preterm infants are among the most heavily transfused patient populations. In 1991, it was estimated that infants with a birth weight of <1.5 kg received ~300 000 red blood cell (RBC) transfusions annually,[1] and infants were typically exposed to 8 to 10 donors each.2

In recent years, efforts to reduce the number of transfusions have succeeded in some cases,[3-6] but large variation in transfusion practices exists among NICUs.[7-9] Moreover, there is little information on the safety of reducing transfusions by tolerating lower hemoglobin levels. Some cohort studies have shown increased cardiac output and oxygen consumption in anemic infants, with return of 1 or both of these values to normal after RBC transfusion.[10-13]

However, a recent study showed echocardiographic abnormalities in anemic infants that persisted for >24 hours after RBC transfusion.[14] Several studies have shown decreased frequency of apnea after transfusion of anemic infants,[15-18] although the same result has been seen after infusion of albumin.[19] One study showed increased blood pressure and improved oxygenation 12 hours after RBC transfusion in mechanically ventilated preterm infants.[20]

The few clinical trials examining this issue provide no clear guidance in deciding when small preterm infants should receive RBC transfusions.21-24 Although these studies varied in design and lacked power to assess important end points, more liberal transfusion was associated with less frequent severe apnea in 1 study22 and faster weight gain in another.[23] To provide additional guidance in transfusion decisions for preterm infants, we conducted a randomized, clinical trial comparing 2 sets of guidelines (ie, “transfusion triggers”) for RBC transfusion of small preterm infants. The guidelines were based on the hematocrit threshold levels for transfusion, ie, the hematocrit level below which an RBC transfusion is dictated by study protocol. The hypothesis was that infants managed with more restrictive transfusion criteria would require fewer transfusions but have no excess of adverse outcomes compared with the infants transfused more liberally.

METHODS

This study was approved by the institutional review board of the University of Iowa. Informed consent was obtained in writing from 1 or both parents of each subject.

Patients

The patients enrolled were preterm infants with birth weight between 500 and 1300 g. Infants were excluded if they had alloimmune hemolytic disease, congenital heart disease (including significant patent ductus arteriosus), other major birth defect requiring surgery, or a chromosomal abnormality. They also were excluded if they were thought to face imminent death, their parents expressed strong philosophical or religious objections to transfusion, or they had received >2 transfusions before they could be enrolled. Infants participating in other clinical studies were excluded if their participation had the potential to interfere with this study by affecting its conduct or outcome.

Study Design

Subjects were stratified by birth weight among 3 groups: 500 to 750, 751 to 1000, and 1001 to 1300 g. Within each of these 3 strata, infants were allocated randomly to the “liberal” or “restrictive” program for RBC transfusion by using a balanced randomization scheme with 3

boxes of numbered, sealed envelopes, 1 box for each birth weight group. On enrollment, an infant received his or her treatment allocation by being assigned the next envelope for the appropriate birth weight stratum. The envelopes were prepared by the principal investigator (E.F.B.) from random-number tables before initiation of the study. Within each stratum, the randomization scheme was adjusted so that the number of infants assigned to each transfusion group was equal after the enrollment of every 4 infants within the stratum. This stratification by birth weight was used to guard against an excess of the smallest infants in 1 transfusion group, because the number of transfusions received is a decreasing function of birth weight. The research nurses (G.A.C., K.J.J., and several others) enrolled the participants and opened the envelopes to determine treatment assignments.

RBC transfusions were given only when the hematocrit level fell below the assigned value. The transfusion threshold levels for each treatment group consisted of 3 steps in hematocrit level, which became lower as the subjects progressed through 3 phases of clinical condition based on respiratory status. The requirement for respiratory support was used as a simplified indicator of overall condition. The use of lower transfusion threshold levels as the infants' condition improved reflected the widely held belief that older, more stable infants could safely tolerate lower hematocrit levels. While tracheally intubated for assisted ventilation (phase 1), infants in the liberal- and restrictive-transfusion groups received an RBC transfusion if their hematocrit levels fell to <46% and <34%, respectively. While receiving nasal continuous positive airway pressure or supplemental oxygen (phase 2), their hematocrit levels were kept at >38% and >28%, respectively, and if requiring neither positive pressure nor oxygen (phase 3), they were kept at >30% and >22%, respectively. These threshold levels were developed by diverging above and below the hematocrit levels most commonly used to trigger transfusions in our unit at the time the study was designed. The threshold levels were set at the highest or lowest hematocrit level with which the faculty neonatologists were comfortable in the context of a clinical trial.

Hematocrit levels were measured from arterial blood samples (from infants with indwelling arterial catheters) or from capillary blood collected from free-flowing heel punctures, which were performed by using an automated capillary-sampling device (Tenderfoot Preemie or Tenderfoot Micro-preemie; ITC, Edison, NJ).25 Approximately 90% of the samples in each group were capillary. Hematocrit levels were obtained each morning in phase 1, 3 times per week in phase 2, and 2 times per week in phase 3. If the hematocrit level was below the transfusion threshold, it was repeated. If both determinations were below the threshold level, a 15 mL/kg transfusion of RBCs, concentrated by centrifugation (hematocrit typically 80–85%), was ordered and given by continuous infusion using a syringe pump over 5 hours. A single-donor transfusion program was in effect during most of the period of this trial.26 For infants in both the liberal- and restrictive-transfusion groups, additional RBC transfusions were allowed at the discretion of the attending neonatologist in the following circumstances: congestive heart failure without other explanation and therefore ascribed to anemia; acute hemorrhage and presumed hypovolemia; frequent or severe apnea refractory to drug treatment (at least 12 episodes in a 12-hour period or 2 episodes within 24 hours requiring increased respiratory support); or request by a surgeon or anesthesiologist for preoperative transfusion. None of the infants received erythropoietin.

Cranial ultrasound examinations were performed according to the protocol used in our NICU. Ultrasound examinations were performed at 7 days of age in all infants and at 14 and 42 days of age in infants who were born at <27 weeks' gestation or who had an abnormal cranial ultrasound examination at 7 days of age. Additional weekly examinations were performed as indicated for infants with progressive changes such as posthemorrhagic hydrocephalus. All 100 subjects had day-7 ultrasound examinations, and 52 (24 liberal; 28

restrictive) had day-42 examinations. The radiologists who interpreted the ultrasound examinations were not aware that the infants were enrolled in a research study.

Outcomes

The following outcomes were tracked and recorded for each subject: number of RBC transfusions; number of RBC donors; survival to discharge; occurrence of patent ductus arteriosus; germinal matrix or intraventricular hemorrhage (graded according to Papile et al27); periventricular leukomalacia; retinopathy of prematurity; bronchopulmonary dysplasia by 2 definitions (oxygen dependence at postnatal age 1 month and oxygen dependence at postmenstrual age 36 weeks, in both cases with compatible radiologic findings); duration of assisted ventilation; duration of supplemental oxygen therapy; number and frequency of all apnea episodes of ≥20 seconds (as detected by the cardiorespiratory monitor and recorded by the bedside nurse); number and frequency of apnea episodes requiring tactile stimulation; number and frequency of apnea episodes requiring assisted ventilation; drug treatment for apnea; number of apnea episodes during the 24-hour periods before and after each transfusion; time to regain birth weight; time to double birth weight; and length of hospitalization.

In addition, various laboratory analyses and physiologic measurements were performed before the first transfusion given (according to the study criteria) after the age of 6 weeks. The first transfusion after 6 weeks of age was chosen as the standard time for these measurements in an effort to balance 2 criteria. First, 6 weeks was sufficiently long after birth to allow physiologic adaptation to the prescribed transfusion program. Second, most subjects would still be patients in the NICU at this age. Performing these measurements before a transfusion assured that the results would not be influenced by a recent transfusion. The samples for analysis were collected and the physiologic measurements were performed once it was determined that the subject would receive a transfusion while the RBCs for transfusion were being prepared and delivered from the blood bank. These studies were hemoglobin, hematocrit, reticulocyte count, oxygen saturation (by pulse oximetry), cardiac output (by echocardiography), blood lactic acid, plasma erythropoietin, and serum ferritin.

Analyses for hemoglobin, hematocrit, reticulocyte count, and blood lactic acid were performed in the hospital's laboratories. The reticulocyte counts were performed by using a fluorescence-activated cell sorter (Technicon H*3; Bayer Diagnostics, Tarrytown, NY). Oxygen saturation was monitored continuously by pulse oximetry (N-200 or N-395; Nellcor, Hayward, CA) during measurements of cardiac output. The mean oxygen saturation was calculated for the period during which cardiac output was being measured. Cardiac output was determined by using 2-dimensional and pulsed Doppler echocardiography.28,29 No attempt was made to measure cardiac output in infants with significant flow through a patent ductus arteriosus or an interatrial shunt. Arterial oxygen content and systemic oxygen transport were calculated, assuming the in vivo oxygen-carrying capacity of hemoglobin to be 1.34 mL/g. Plasma erythropoietin levels were determined by using a double-antibody radioimmunoassay.30 Serum ferritin levels were performed by radioimmunoassay using a commercial kit (Quantimune Ferritin IRMA kit; Bio-Rad Laboratories, Hercules, CA). Laboratory assays and interpretation of the echocardiographic studies were done without knowledge of the patients' treatment assignments.

Sample-Size Determination and Statistical Analysis

In the late 1980s, very low birth weight infants in our hospital received an average of 7 to 10 RBC transfusions with an SD similar in magnitude to the mean.[1,3] We computed the sample size needed for this study to be able to detect a difference in the mean number of transfusions equal to ½ SD with $\alpha = .05$ and $\beta = .20$. For example, we wished to be able to

detect a difference between 8 transfusions per infant in the liberal-transfusion group and 4 transfusions per infant in the restrictive-transfusion group, assuming a pooled SD of 8. This analysis produced a required sample of 49 infants per group, for a total of 98.[31] By the time the study began, our nonstudy very low birth weight infants were receiving fewer transfusions, but the SD had also become smaller.[3] The sample-size estimation remained valid, however, because a sample of 49 infants per group would still allow us to detect a difference of ½ SD, although the mean number of transfusions was lower. With fewer transfusions, for example, a sample of 98 infants would enable us to show a difference between 4 and 2 transfusions per infant with an SD of 4. All infants were analyzed with the group to which they were assigned at enrollment.

The liberal- and restrictive-transfusion groups were compared with respect to all recorded outcomes. Survival times, ie, times required to reach certain events (eg, time to regain birth weight), were compared by using the log-rank test. Other continuous variables were analyzed by using the unpaired *t* test or, for nonparametric variables, the Wilcoxon test. Dichotomous outcomes were compared by using Fisher's exact test. All analyses were 2-sided. The composite outcome of grade 4 (intraparenchymal) brain hemorrhage or periventricular leukomalacia (or both) was examined as a measure of major adverse neurologic events. To allow comparison of the treatment groups with respect to this composite outcome, it was assumed that infants without late cranial ultrasound examinations did not have periventricular leukomalacia.

The short-term impact of RBC transfusion on the frequency of apnea was examined in the 2 transfusion groups by using data from all transfusions. The number of apnea episodes during the 24 hours before and after each transfusion was tabulated, and the change in apnea frequency after transfusion was analyzed within each group, liberal and restrictive. Negative binomial regression analysis was employed, using the method of generalized estimating equations. The independent variables in the model included transfusion group (liberal or restrictive), time (before or after), and group-time interaction. This method was used to account for the correlation among observations from the same subject, because most subjects had >1 transfusion.

An interim analysis of the accumulated data was planned before the study began and was conducted halfway through the study, after 49 subjects had been enrolled and their major short-term outcomes known. This analysis revealed no major differences in serious adverse events; thus, the study was continued until at least 49 infants had been studied in each group.

RESULTS

Patients Enrolled

During the period of enrollment (December 1, 1992, through June 2, 1997), 439 infants with a birth weight of 500 to 1300 g were admitted to our NICU, of whom 216 met all eligibility criteria (Fig 1). The parents of 7 eligible infants were not approached: in 5 cases because the infants were expected to be transferred soon to another hospital and in 2 cases because no research team member was available to seek consent. The parents of 106 infants declined participation. Thus, 103 infants were initially enrolled in the study. Three of these infants died within 48 hours of enrollment and were dropped from the study (2 who had been assigned to the liberal-transfusion group and 1 who had been assigned to the restrictive-transfusion group). This left a total of 100 infants who continued in the study and are included in the analysis: 51 in the liberal-transfusion group and 49 in the restrictive-transfusion group. The demographic characteristics of the infants in the 2 treatment groups were similar (Table 1), although the liberal-transfusion group had a lower fraction of male infants (41% vs 61%; $P = .049$). The median age of enrollment was 3 days in each group.

Transfusions and Donor Exposures

The 51 infants in the liberal-transfusion group received a total of 266 RBC transfusions, including 21 transfusions given before enrollment; 6 infants in this group (12%) received no transfusions. The 49 infants in the restrictive-transfusion group received a total of 161 RBC transfusions, including 27 given before enrollment; 5 infants in this group (10%) received no transfusions. Counting all RBC transfusions, including those given before enrollment, infants in the liberal-transfusion group received more transfusions per infant ($P = .025$; mean ± SD: 5.2 ± 4.5) than those in the restrictive-transfusion group (mean: 3.3 ± 2.9); the median number of transfusions was 4 in the liberal-transfusion group and 2 in the restrictive-transfusion group (Table 2). When only RBC transfusions during the study period are included, the difference was even more significant ($P = .006$), with the infants in the liberal-transfusion group receiving a mean of 4.8 ± 4.1 transfusions, compared with 2.7 ± 2.4 in the restrictive-transfusion group; the medians again were 4 and 2.

Including RBC transfusions given before enrollment, the number of donors per infant was not statistically different ($P = .082$; mean ± SD: 2.8 ± 2.5 in the liberal-transfusion group vs 2.2 ± 2.0 in the restrictive-transfusion group); the median number of donors was 2 in both groups (Table 2). Considering only the transfusions given during the study, there was also no difference ($P = .079$; mean number of donors: 2.5 ± 2.5 in the liberal-transfusion group versus 1.8 ± 1.8 in the restrictive-transfusion group); the median number of donors again was 2 in both groups.

Nineteen RBC transfusions were given that did not meet the study criteria for transfusion. Two of these were in the liberal-transfusion group, and 17 were in the restrictive group. In 7 cases, infants met the study criteria for an RBC transfusion but were not transfused. In each of these 7 cases, the infant was in the liberal-transfusion group. The age at first transfusion was higher in the restricted transfusion group (median: 8 vs 3 days), although this difference was not statistically different ($P = .117$).

Clinical Outcomes

There was no difference in survival or in the risk of patent ductus arteriosus, retinopathy of prematurity, or bronchopulmonary dysplasia (Table 3). There was no difference in the time on assisted ventilation, the time on supplemental oxygen, the time required to regain birth weight, the time to double birth weight, or the length of hospitalization.

There was no difference in the risk of germinal matrix or intraventricular hemorrhage of all grades or of grades 3 and 4 combined (Table 3). The restrictive-transfusion group had more infants with grade 4 hemorrhage, ie, parenchymal brain hemorrhage (4 vs 0; $P = .054$). There were also more infants in the restrictive group with periventricular leukomalacia (4 vs 0), although this difference was not statistically significant ($P = .115$). The 4 infants with periventricular leukomalacia presented with periventricular areas of increased echogenicity at ≤14 days; these areas subsequently evolved to cystic periventricular leukomalacia in all 4 cases. The number of infants who suffered severe adverse brain events (intraparenchymal brain hemorrhage, periventricular leukomalacia, or both) was higher in the restrictive group (6 vs 0; $P = .012$). Two infants in the restrictive-transfusion group had both parenchymal brain hemorrhage and periventricular leukomalacia.

Infants in the restrictive-transfusion group had significantly more apnea than did those in the liberal-transfusion group (Table 4), including greater frequency of apnea (median: 0.84 vs 0.43 episodes per day; $P = .004$), more episodes of apnea requiring tactile stimulation (median: 0.42 vs 0.23 episodes per day; $P = .002$), and more episodes requiring positive-pressure ventilation (median: 0.02 vs 0 episodes per day; $P = .070$). Infants in the restrictive-transfusion group had a decrease in the frequency of apnea after RBC transfusion, from a

mean of 1.40 ± 0.25 to 0.63 ± 0.09 episodes per day (P = .003); infants in the liberal-transfusion group did not, with a mean of 0.85 ± 0.21 vs 0.63 ± 0.13 episodes per day (P = .233).

Physiologic Measurements

At the time of the first RBC transfusion after 6 weeks of age, the hemoglobin, hematocrit, arterial oxygen content, and systemic oxygen transport values were significantly higher in the liberal-transfusion group (Table 5). Reticulocyte count and cardiac output were not significantly different. Plasma erythropoietin concentration was higher in the restrictive-transfusion group (P = .037), but blood lactic acid was not significantly different. Serum ferritin was higher, but not significantly so, in the liberal-transfusion group (478 vs 279 μg/L; P = .108).

DISCUSSION

In this randomized clinical trial comparing liberal-and restrictive-transfusion programs for preterm infants, we confirmed that the number of transfusions can be reduced by using restrictive transfusion criteria. However, the number of donors to whom the infants were exposed was not reduced, nor were more infants able to avoid transfusion completely. Infants in the restrictive-transfusion group were more likely to suffer major adverse neurologic events (parenchymal brain hemorrhage, periventricular leukomalacia, or both) and had more frequent apnea. The frequency of apnea was nearly twice as high in the restrictive-transfusion group; although this difference is statistically significant, the absolute increase in the frequency of apnea, <1 event per day, was so small as to be of questionable clinical importance. Nevertheless, increased apnea may adversely affect neurodevelopmental outcome. Preterm infants with apnea after discharge documented by home monitoring have been shown to have lower Mental Developmental Index values at the corrected age of 1 year compared with infants without apnea.[32]

The groups were similar in birth weight, gestational age, and other known risk factors except for gender; there was an excess of male infants in the restrictive-transfusion group. Male gender has not been clearly identified as a risk factor in apnea, intracerebral hemorrhage, or periventricular leukomalacia. However, because male gender is a risk factor for other adverse outcomes associated with premature birth, the greater number of males in the restrictive-transfusion group cannot be ruled out as a confounding factor contributing to the increased frequency of apnea and adverse neurologic events in this group.

Although a cause-and-effect relationship was not proven by the results of this study, the difference in adverse neurologic events between the liberal- and restrictive-transfusion groups is of great concern. Infants in the restrictive-transfusion group had lower systemic oxygen transport and, presumably, lower oxygen delivery to various organs, likely including the brain. Decreased oxygen delivery to the brain may be the mechanism for the increased frequency of brain injury and the more frequent apnea in the infants who received an RBC transfusion with more restrictive criteria. The increase in severe brain hemorrhage in the restrictive-transfusion group may have resulted from increased cerebral blood flow in partial compensation for the decreased arterial oxygen content in this group.

It is not known whether the excess in short-term adverse neurologic events seen with restrictive use of RBC transfusions in study infants will result in increased long-term problems with brain function in later life. However, the results of this study suggest that the growing use of restrictive RBC-transfusion criteria for preterm infants in clinical practice is not without cost and should be reexamined carefully.

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ABBREVIATION

RBC	red blood cell

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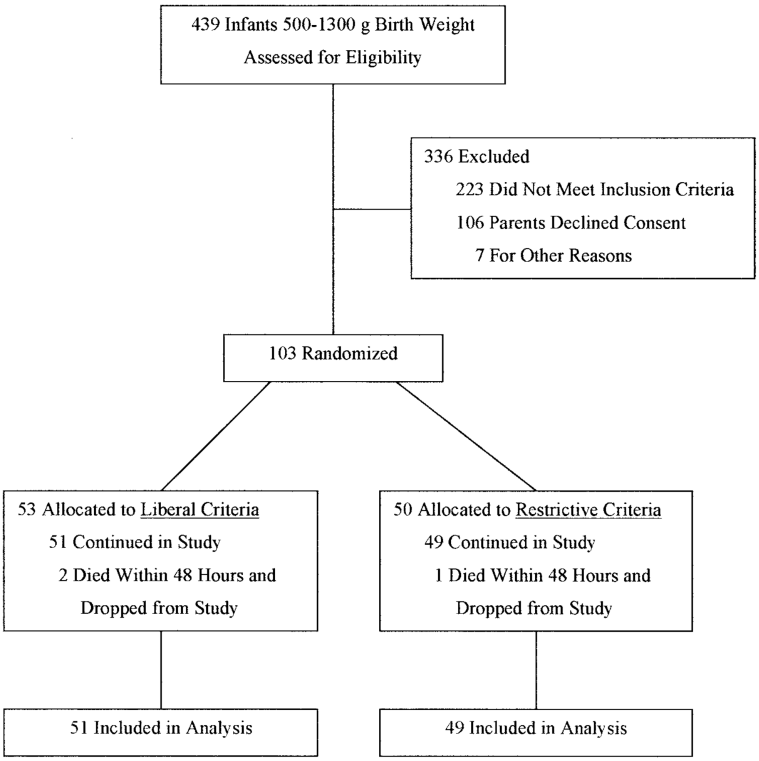

Fig 1.
Profile of infant enrollment and participation.

TABLE 1

Demographic Characteristics

	Liberal-Transfusion Group (*n* = 51)	Restrictive-Transfusion Group (*n* = 49)
Birth weight, g, mean ± SD	954 ± 193	958 ± 194
Gestational age, wk, mean ± SD	27.8 ± 2.1	27.7 ± 1.7
Male, *n* (%)	21 (41)	30 (61)*
Mother's race or ethnic group, *n* (%)		
White	39 (76)	40 (82)
Black	7 (14)	4 (8)
Hispanic	3 (6)	4 (8)
Asian	1 (2)	1 (2)
Other or unknown	1 (2)	0 (0)
Multiple birth, *n* (%)		
Twins	11 (22)	14 (29)
Triplets	2 (4)	4 (8)
Born at University of Iowa Hospitals and Clinics, *n* (%)	43 (84)	47 (96)
Apgar score at 1 min, median (interquartile range)	4 (3–6)	5 (2–6)
Apgar score at 5 min, median (interquartile range)	7 (5–8)	7 (6–8)
Initial hematocrit, %	50 ± 8	49 ± 8

*$P = .049$.

TABLE 2

RBC Transfusions and Donor Exposures

	Liberal-Transfusion Group (*n* = 51)	Restrictive-Transfusion Group (*n* = 49)	*P*
Infants receiving no transfusions, *n* (%)	6 (12)	5 (10)	1.0
Transfusions per infant, before and during study			
Mean ± SD	5.2 ± 4.5	3.3 ± 2.9	
Median (interquartile range)	4 (2–8)	2 (2–5)	.025
Transfusions per infant, during study			
Mean ± SD	4.8 ± 4.1	2.7 ± 2.4	
Median (interquartile range)	4 (2–8)	2 (1–4)	.006
Donor exposures per infant, before and during study			
Mean ± SD	2.8 ± 2.5	2.2 ± 2.0	
Median (interquartile range)	2 (1–4)	2 (1–2)	.082
Donor exposures per infant, during study			
Mean ± SD	2.5 ± 2.5	1.8 ± 1.8	
Median (interquartile range)	2 (1–4)	2 (1–4)	.079
Age at first transfusion (of those transfused), d, median (interquartile range)	3 (1–14)	8 (1.25–20)	.117

TABLE 3

Clinical Outcomes

	Liberal-Transfusion Group (*n* = 51)	Restrictive-Transfusion Group (*n* = 49)	*P*
Survived to discharge, *n* (%)	50 (98)	47 (96)	.614
Patent ductus arteriosus, *n* (%)			
Indomethacin treatment	20 (39)	15 (31)	.407
Surgical closure	2 (4)	4 (8)	.432
Intraventricular hemorrhage, *n* (%)			
Any grade, 1–4	17 (33)	14 (29)	.669
Grade 3 or 4	8 (16)	5 (10)	.555
Grade 4	0 (0)	4 (8)	.054
Periventricular leukomalacia, *n* (%)	0 (0)	4 (14)	.115
Intraventricular hemorrhage, grade 4, or periventricular leukomalacia, *n* (%)	0 (0)	6 (12)	.012
Retinopathy of prematurity, *n* (%)			
Total	27 (60)	22 (51)	.520
≥ Stage 3	2 (4)	2 (4)	1.0
Laser treatment	0 (0)	1 (2)	.490
Bronchopulmonary dysplasia, *n/N* (%)			
Oxygen dependence at 28 d	19/50 (38)	17/48 (35)	.836
Oxygen dependence at 36 wk	20/50 (40)	13/45 (29)	.287
Time on ventilator or CPAP, d, median (interquartile range)	40 (19–59)	39 (31–58)	.692
Time on supplemental oxygen, d, median (interquartile range)	34 (5–73)	26 (9–63)	.704
Time to regain birth weight, d, median (interquartile range)	13 (9–15)	13 (9–16)	.990
Time to double birth weight, d, median (interquartile range)	59 (54–64)	60 (54–68)	.698
Length of hospitalization, d, median (interquartile range)	74 (54–96)	73 (62–95)	.392

CPAP indicates continuous positive airway pressure.

TABLE 4

Apnea of Prematurity

	Liberal-Transfusion Group (*n* = 51)	Restrictive-Transfusion Group (*n* = 49)	*P*
Subjects with no apnea, *n* (%)	2 (4)	0 (0)	.495
Subjects with >1 apnea episode per d, *n* (%)	10 (20)	21 (43)	.017
Subjects with apnea receiving methylxanthine treatment, *n* (%)	47 (94)	46 (94)	1.0
Apnea episodes (>20 sec), median (interquartile range)	32 (10–61)	52 (30–87)	.004
Apnea episodes (>20 sec) per d, median (interquartile range)	0.43 (0.15–0.85)	0.84 (0.54–1.50)	.004
Apnea episodes requiring stimulation, median (interquartile range)	15 (4–33)	25 (14–48)	.006
Apnea episodes requiring stimulation per d, median (interquartile range)	0.23 (0.06–0.51)	0.42 (0.19–0.83)	.002
Apnea episodes requiring ventilation, median (interquartile range)	0 (0–3)	1 (0–9)	.113
Apnea episodes requiring ventilation per d, median (interquartile range)	0 (0–0.04)	0.02 (0–0.14)	.070
Apnea episodes in 24 h before transfusion (mean ± SD)	0.85 ± 0.21	1.40 ± 0.25	
Apnea episodes in 24 h after transfusion (mean ± SD)	0.63 ± 0.13*	0.63 ± 0.09†	

*P = .233, before versus after transfusion.

†P = .003, before versus after transfusion.

TABLE 5

Physiological Measurements, Before Transfusion at 6 Weeks of Age (Mean ± SD)

	Liberal-Transfusion Group (n = 24)	Restrictive-Transfusion Group (n = 15)	P*
Hemoglobin, g/dL, mean ± SD	11.0 ± 1.9	8.3 ± 1.1	<.0001
Hematocrit, %, mean ± SD	32 ± 6	26 ± 5	<.0001
Reticulocyte count, per nL, mean ± SD	91 ± 58	120 ± 51	.064
Cardiac output, mL/min per kg, mean ± SD	313 ± 123	291 ± 122	.941
Arterial oxygen content, mL/dL, mean ± SD	14 ± 3	11 ± 1	<.0001
Systemic oxygen transport, mL/min per kg, mean ± SD	43 ± 17	31 ± 11	.035
Blood lactic acid, mEq/L, mean ± SD	1.2 ± 0.4	1.5 ± 0.8	.556
Plasma erythropoietin, U/mL, mean ± SD	14 ± 4	18 ± 8	.037
Serum ferritin, μg/L, median (interquartile range)	478 (306–638)	279 (214–366)	.108

* The unpaired t test was used except for serum ferritin, for which the Wilcoxon rank-sum test was used.