Published in final edited form as:
Pediatrics. 2005 May ; 115(5): 1299–1306. doi:10.1542/peds.2004-1680.

Reduction in Red Blood Cell Transfusions Among Preterm Infants: Results of a Randomized Trial With an In-Line Blood Gas and Chemistry Monitor

John A. Widness, MD[*], **Ashima Madan, MD**[‡], **Ligia A. Grindeanu, MD**[*], **M. Bridget Zimmerman, PhD**[§], **David K. Wong, PhD**[‖], and **David K. Stevenson, MD**[‡]

[*]Department of Pediatrics, College of Medicine, College of Public Health, University of Iowa, Iowa City, Iowa

[§]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa

[‡]Department of Pediatrics, Stanford University School of Medicine, Stanford, California

[‖]Independent consultant, Del Mar, California.

Abstract

Background—Critically ill, extremely premature infants develop anemia because of intensive laboratory blood testing and undergo multiple red blood cell (RBC) transfusions in the early weeks of life. To date, researchers have had only limited success in finding ways to reduce transfusions significantly in this patient population.

Objective—To reduce RBC transfusions for these infants by using a point-of-care bedside monitor that returns analyzed blood to the patient.

Design, Setting, and Patients—This was a prospective, 2-center, randomized, open, controlled, clinical trial with a 1:1 assignment of extremely low birth weight infants (weighing 500–1000 g at birth) to control or monitor groups and analysis with the intention-to-treat approach. Predefined RBC transfusion criteria were applied uniformly in the 2 groups.

Interventions—Clinical treatment of study subjects with an in-line, ex vivo, bedside monitor that withdraws blood through an umbilical artery catheter, analyzes blood gases and sodium, potassium, and hematocrit levels, and returns the sample to the patient.

Main Outcome Measures—The total volume and number of RBC transfusions during the first 2 weeks of life and the total volume of blood removed for laboratory testing.

Results—The trial was terminated prematurely when one center's NICU changed its standard method of laboratory testing. In the first 2 weeks of life, there was a nonsignificant 17% lower cumulative RBC transfusion volume in the monitor group ($n = 46$), compared with the control group ($n = 47$). However, data from the first week only (the period of greater catheter use) demonstrated a significant 33% lower cumulative RBC transfusion volume in the monitor group. Cumulative phlebotomy loss was ~25% less in the monitor group throughout the 2-week study period. There was no difference between groups in neonatal mortality, morbidity, and neurodevelopmental outcome

Address correspondence to John A. Widness, MD, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, 8807 JPP, Iowa City, IA 52242-1083. john-widness@uiowa.edu.

Dr Wong was the principal inventor of the in-line blood gas and chemistry monitor used in this study.

No conflict of interest declared.

rates at 18 to 24 months. This is the first randomized trial documenting that RBC transfusions administered to neonates can by reduced by decreasing laboratory phlebotomy loss.

Conclusions—As long as an umbilical artery catheter is available for blood sampling with an in-line blood gas and chemistry monitor, significant reductions in neonatal RBC transfusions can be achieved. The patients most likely to benefit from monitor use are the smallest, most critically ill newborns.

Critically ill, extremely low birth weight (ELBW), preterm infants who weigh 500 to 1000 g at birth are among the most highly transfused groups of patients, because of the anemia they routinely experience.[1] Although there has been a trend toward fewer red blood cell (RBC) transfusions for this group,[2–4] the few randomized trials that have been conducted have neither explained this phenomenon nor achieved major reductions in neonatal blood transfusions.

Approximately one half of all RBC transfusions administered to ELBW infants before discharge are given in the first 2 weeks of life, when neonatal cardiorespiratory illness is most severe and laboratory blood testing is greatest.[4] Weekly phlebotomy loss among preterm infants during this period averages 10% to 30% of total blood volume (10–25 mL/kg). The fact that the total blood volume removed is highly correlated with the volume transfused[5] strongly suggests a causal relationship, providing the rationale for developing strategies to decrease phlebotomy blood loss in the early postnatal period as a way of reducing RBC transfusions among preterm infants.

Use of laboratory blood-testing devices operated at the bedside of critically ill ELBW newborns, to “keep the blood in the infant,” is one such strategy.[6] Recent technologic innovations in the design and fabrication of biosensors and microprocessors have led to the development of 2 types of low-volume, highly accurate, point-of-care (POC) devices with short analytic turnaround times and little or no pre-analytic error.[7] POC blood-testing devices that require the permanent removal of blood are categorized as “analyzers,” whereas those that either return blood to the infant after analysis or do not require blood removal are referred to as “monitors.” It is clear that monitors offer greater potential for reducing the volume and number of neonatal RBC transfusions.

In this study, we hypothesized that ELBW premature infants treated with an umbilical artery catheter (UAC) attached to an in-line, ex vivo, POC monitor capable of analyzing blood gases and sodium, potassium, and hematocrit levels would experience a 35% reduction in the RBC volume transfused during the first 2 weeks of life. To address this hypothesis, a 2-center, randomized, open, controlled, clinical trial with equal assignment of infants to routine care or to care using an in-line monitor was conducted. Standardized RBC transfusion criteria and blood administration procedures were uniformly applied.

METHODS

Hypothesis

We hypothesized that the volume of RBCs transfused per kilogram of body weight during the first 2 weeks of life would be reduced by 35% among critically ill ELBW infants treated with a UAC for blood sampling and clinical monitoring, because of the monitor's potential for reducing laboratory blood loss. A 2-week study period was chosen because our retrospective data showed that the duration of UAC use averaged 7 days at both sites, and we wanted to include the potential benefit from the continuing but declining use of the monitor during week 2. The device used was an in-line, ex vivo monitor (VIA-LVM blood gas and chemistry monitoring system; VIA Medical, Austin, TX) that self-calibrates every 30 minutes with an isotonic saline/electrolyte solution.[8] On the command of the operator, the monitor automatically withdraws 1.5-mL blood samples through the UAC, analyzes the samples for

blood gases and sodium, potassium, and hematocrit levels, and then reinfuses all except 25 μL of blood.

Study Population and Enrollment Criteria

The institutional review boards at both centers approved the study. Preterm infants eligible for study were those <24 hours of age, with birth weights between 500 and 1000 g, who had a UAC inserted as clinically indicated. Infants were excluded if the maternal prenatal antibody testing indicated the presence of immune hemolytic disease, if the infant was enrolled in a competing research study in which receiving RBC transfusions was an important outcome measure, if the infant had hydrops or a life-threatening congenital anomaly, or if the infant's condition was deemed incompatible with survival (≤22 weeks of gestation, trisomy 13, or trisomy 18).

Standard Laboratory Practices at Study Sites

Conventional laboratory blood analyses of pH, blood gases, and electrolyte levels in both NICU laboratories were performed with benchtop analyzers (model ABL-625 at site A and model ABL-505 at site B; Radiometer America, Westlake, OH). Decisions regarding the timing of UAC removal were left to the attending physicians.

Treatment Protocol

The study was conducted as a prospective, randomized, unmasked, 2-center, controlled trial. Study participants were assigned to either the control group or the monitor group depending on whether conventional or in-line monitor analysis of pH, partial pressure of carbon dioxide, partial pressure of oxygen, and sodium, potassium, and hematocrit levels was performed. Decisions regarding blood test ordering were the responsibility of the attending physicians, with the following exceptions: (1) protocol-mandated hematocrit determinations were performed a minimum of 3 times per week (unless already ordered clinically); (2) plasma ferritin measurements were performed at study entry and completion; (3) paired laboratory-comparison blood samples were drawn for monitor group subjects once daily, to confirm the accuracy of the monitor; and (4) monitor and laboratory paired samples were drawn if monitor results exceeded accepted critical outlier limits.[7]

The study mandated adherence to uniform RBC transfusion criteria based on hematocrit values and severity of illness (Table 1); compliance was monitored daily by study nurses, who recorded violations. Individual transfusions were administered from adult, multiuse, donor RBC units containing extended storage medium; the transfusions consisted of packed RBCs administered as ~13 mL/kg packed RBCs over 3 to 4 hours (achieved at one site through administration of 15 mL/kg packed RBCs with a hematocrit value of 85% and at the other site through administration of 20 mL/kg packed RBCs with a hematocrit value of 65%).

Randomization

Subjects were randomized with permuted blocks from a computer-generated random number table. Informed written parental consent was obtained before randomization. Assignment to control or monitor groups was performed with 1:1 treatment allocation, with stratification according to study center and according to birth weight (with 500- to 750-g and 750- to 1000-g subgroups). After informed consent was obtained, research personnel assigned subjects to study groups by drawing opaque envelopes consecutively.

Data Collection

Demographic data were extracted from hospital records for maternal and infant outcomes and morbidities, as defined by the National Institute of Child Health and Human Development

Neonatal Network.[9-11] At both sites, laboratory blood gas and electrolyte instruments were interfaced with hospital computer information systems, the data from which were included in the study results. Daily laboratory blood loss per kilogram was estimated on the basis of the hospital computer/research nurses' records, by using the laboratory-specified volume of blood required for each type of analysis. To correct for predicted underestimates, phlebotomy loss was increased by 19%.12

Neurodevelopmental records were obtained at both sites for study subjects enrolled in the 18- to 24-month infant follow-up program, although participation in the program was not a requirement for study enrollment. Study subjects were evaluated for cerebral palsy and vision and hearing problems; they also underwent Bayley testing, performed at adjusted age of 18 months at one site and 24 months at the other.

Determination of Sample Size

Sample size determination was based on retrospectively collected RBC transfusion and phlebotomy data for ELBW infants at both study sites. The mean (± SD) volume of RBCs transfused per kilogram in the first 2 weeks of life for a 12-month period before the study was 47.4 ± 29.6 mL/kg (n = 76). On the basis of previous reports of blood loss attributable to the VIA monitor,[12] we estimated a 50% reduction in laboratory phlebotomy loss among ELBW infants,[13] which we decreased to 35% because of the additional blood needed for daily paired-sample validation of monitor values and for confirmation of critical outliers. Because the volume of blood transfused approximates that removed for laboratory testing among infants, [5] we anticipated a concomitant and clinically important 35% reduction in the volume of RBC transfusions during the first 2 weeks of life. To detect this reduction at the 5% level of significance, with 2-sided testing and a power of 80%, 51 subjects were required for each treatment group.[14] To allow for study attrition attributable to death or study withdrawal, an additional 13 infants per group were required.

Statistical Methods

Statistical analysis was performed with the SAS program (SAS Institute, Cary, NC). Data were analyzed according to the intention to treat, with the use of a linear mixed-model analysis for repeated measures to test for differences in the mean cumulative total volume of RBCs transfused per kilogram of body weight after 3, 7, 10, and 14 days of life, with adjustment for the effect of catheter use duration and study site. The same analysis was used to compare mean cumulative phlebotomy loss. Because these 2 outcome measures were not normally distributed, a logarithmic transformation was applied to the data before analysis. The model-adjusted, least-squares mean estimates obtained from the analysis of the transformed data were then back-transformed, so that the adjusted mean ± SEM estimates are reported with the original scale. To account for the multiple tests that compared between-group means at each time point (4 tests) and for site-specific comparisons (8 tests, ie, 4 tests at each of the 2 sites), the P values were adjusted with Bonferroni's method. The demographic and clinical baseline and outcome variables, ie, frequency and percentages for the categorical variables, mean ± SD for the normally distributed variables, and median and 25th to 75th percentile range for the non-normally distributed continuous variables, were compared with the 2-sample t test or Wilcoxon rank-sum test for the continuous variables and the χ^2 test and Fisher's exact test for the categorical variables. A value of $P < .05$ was considered statistically significant.

RESULTS

Recruitment and Participants

This clinical trial was terminated at the halfway point when one center's NICU changed its standard method of laboratory analysis, significantly altering the volume of blood required for

laboratory testing. The reasons for this were entirely attributable to factors unrelated to the present study. During the enrollment period, 196 infants were assessed for study eligibility on the basis only of birth weight of <1000 g, and 130 (66%) met the study inclusion/exclusion criteria (Fig 1). Approximately two thirds (n = 93) were enrolled and randomized to control (n = 47) or monitor (n = 46) groups. Study participants and infants eligible for study but not enrolled (n = 37) were comparable with respect to weight and gestational age at birth, gender, multiple birth, duration of UAC use, and place of delivery, ie, within or outside the 2 centers (data not shown). The most common reason for non-enrollment was parental refusal.

With the exception of 1 infant from the monitor group who died on the first day of life, all study subjects received their allocated treatment. Five infants in both groups died before the end of the 14-day study period. In conformity with the intention-to-treat approach, data for both surviving and nonsurviving infants were included in the primary outcome analysis. Of the 42 conventionally treated infants who survived the 14-day study period, 41 (98%) survived to discharge and were alive at the time of follow-up assessment. Of the 41 monitor group infants who completed the study, 37 (90%) survived to discharge and 36 (88%) survived to the follow-up assessment (P = .41). There were no differences in the causes of death between groups.

Baseline Characteristics of the Mothers and Infants

Maternal data at delivery were similar for the control and monitor groups (Table 2), as were neonatal demographic data at birth and at study entry (Table 3).

RBC Transfusion Volume and Number of Transfusions Administered

At the end of the 2-week study period, there was a moderate but nonsignificant 17% reduction in cumulative RBC transfusion volume per infant in the monitor group versus the control group (38 ± 3 vs 46 ± 4 mL/kg; P = .46), when these data were adjusted for study site and duration of UAC use. However, the data from the first week only, the period during which 53% of all surviving infants still had UACs in use for in-line monitoring, demonstrated a clinically significant 33% reduction in cumulative RBC transfusion volume in the monitor group (22 ± 3 vs 33 ± 3 mL/kg; P = .04) (Fig 2). Cumulative RBC transfusion volume per infant among survivors of both groups, adjusted for site and group, was significantly greater in the first week than in the second (P < .0001). A similar reduction was observed in the cumulative number of RBC transfusions administered to the 2 groups (data not shown), ie, the monitor group received 0.82 (P = .02) and 0.73 (P = .53) fewer RBC transfusions per infant at 1 and 2 weeks of life, respectively. There were no significant differences between the 2 sites when the volume (P = .17) and number (P = .11) of RBC transfusions were compared.

Laboratory Phlebotomy Loss

Modeled cumulative phlebotomy loss data demonstrated significant differences between the 2 study groups throughout the entire study period, with the monitor group having 27% and 24% lower cumulative phlebotomy losses at weeks 1 and 2, respectively (Fig 3A). Cumulative laboratory blood loss was ~60% more at site B, compared with site A (Fig 3B), primarily because of the amount of blood withdrawn per sample, rather than the frequency of sampling. When both groups of survivors were analyzed, cumulative laboratory blood loss adjusted for site and group was significantly greater in the first week than in the second (P < .0001).

Univariate Correlations

When the data from study subjects in both groups were combined, there was a highly significant, linear association between the laboratory phlebotomy loss during the entire study period and the volume of RBCs transfused (r = 0.78; P < .0001). When this relationship was

compared between the 2 study groups with analysis of covariance, no difference was observed ($P = .27$).

Transfusion Protocol Violations

Violations occurred on 7% of study days. Under-and overtransfusions were recorded in both groups, with 81% of these violations representing overtransfusions, ie, administration of a RBC transfusion before the specified criteria were met. The cumulative percentages of days when overtransfusion occurred were similar at weeks 1 and 2 for the control and monitor groups, ie, 4.83 ± 1.64% vs 3.61 ± 1.27% ($P = .55$) for week 1 and 2.72 ± 0.92% vs 5.50 ± 0.88% ($P = .06$) for week 2. There were insufficient under-transfusion violations for meaningful comparison.

Laboratory and Clinical Indicators and Morbidities Before Hospital Discharge

When data were analyzed for all study subjects and for only the infants who survived to discharge, no differences were found between the control and monitor groups in the duration of UAC use, laboratory hemoglobin and ferritin levels, or clinical outcomes and morbidities (Table 4).

Neurodevelopmental Outcomes at Adjusted Age of 18 to 24 Months

Adjusted Bayley Mental Developmental Index and Physical Developmental Index test scores, which were available for 54 of the 77 survivors (70%), showed no significant differences between the control ($n = 25$) and monitor ($n = 23$) groups for those whose scores were ≥70, ie, 91 ± 3.8 vs 90 ± 2.9 for the Mental Developmental Index and 84 ± 2.6 vs 85 ± 3.0 for the Physical Developmental Index. There were no differences in the numbers of subjects with Mental Developmental Index or Physical Developmental Index test scores of <70 or in the other neurodevelopmental outcomes examined, including visual and auditory impairment and cerebral palsy (data not shown).

DISCUSSION

At the time of the premature termination of the study, the cumulative RBC volume transfused at 2 weeks was shown to be only 17% less for monitor group infants on an intention-to-treat basis, rather than the 35% predicted as the primary outcome. However, at the end of the first week only, the period corresponding to greatest severity of illness and therefore greatest UAC use (UACs being a requirement for POC monitor use), the monitor group had experienced significantly less laboratory blood loss (22%) and received significantly less transfusion volume and fewer RBC transfusions (33% and 32% reductions, respectively).

Reduction in RBC Transfusion Volume

Although unanticipated at the outset, it was deemed necessary to stop the study near its midpoint, when the laboratory administration at one of the sites modified its method of testing by changing to another POC device. This change had the potential to significantly affect phlebotomy loss and therefore the primary transfusion outcome. As a result, it was decided to continue the study just until the change was instituted, at which point only 73% of the planned number of study subjects had been enrolled.

Phlebotomy Loss as the Primary Cause of Neonatal Anemia and Need for RBC Transfusion

As noted previously, there is strong evidence in the literature supporting laboratory phlebotomy loss as the primary cause of anemia among premature infants in the weeks immediately after birth, when RBC transfusions are most frequent.[4] This evidence includes the significant

relationship reported between the volume of blood removed for laboratory testing and the volume of RBCs transfused,[5] a relationship also observed in our study.

Additional observations in the present study support a causal relationship between phlebotomy and RBC transfusion needs among newborn infants. First, the significant decrease in transfusions during week 1 of life in the monitor group occurred during the time period when UACs are most frequently used in clinical care (UACs being a requirement for in-line POC blood testing). Second, the results of the univariate analyses of phlebotomy and transfusion volume in both groups demonstrated a highly significant association. Third, multivariate modeling indicated that the duration of UAC use in both groups was associated with both reduced RBC transfusion volume and laboratory phlebotomy loss.

Assessment of Monitor's Potential for Reducing RBC Transfusions

The present study likely understates the potential benefits of in-line ex vivo monitoring, for several reasons. First, there is the “learning curve” issue. Because the physicians and nurses at the 2 sites had not used POC monitoring previously in a clinical setting, they were not practiced in identifying situations that would take full advantage of the monitor's potential for reducing blood loss. For example, specific analyte measurements needed only once per day (eg, calcium) might be combined with the once-daily paired comparison of monitor and benchtop instrument results, thus allowing the same sample to be used for multiple purposes. As experience with the monitor is gained, the need for fewer benchtop confirmatory tests may be reduced, thereby decreasing phlebotomy loss even more.[15]

Second, future technologic improvements may dramatically expand the monitor's potential for reducing phlebotomy loss. The monitor is now capable of performing more than one half of common blood tests, involving ~50% of the volume of blood removed, for ELBW infants during the first weeks of life.[13] If the monitor's capabilities are expanded to include other analytes (eg, glucose, bilirubin, blood urea nitrogen, and creatinine measurements), as is technically feasible with ex vivo devices using electrochemical detection identical to that of benchtop instruments, the potential for additional reductions in blood loss may be greatly enhanced, perhaps equaling as much as 80% of the volume sampled.[13]

Finally, the monitor's clinical benefits are dependent on neonatal transfusion and blood-testing practices. Studies of critically ill adults have provided compelling evidence that increasingly restrictive transfusion practices result in improved mortality and morbidity rates.[16] Similar evidence for neonates is lacking, making it difficult to predict with certainty the direction transfusion practices will take. If the current trend that we and others have observed continues, with fewer transfusions because of more restrictive neonatal transfusion practices,[2-4] and the number and kind of blood tests ordered remain unchanged, then in-line monitoring should become more efficacious in reducing RBC transfusions.

Study Limitations

There are several limitations to this study. First, this was an open study in which it was impossible to disguise the 2 treatment groups, raising the question of possible bias influencing clinical practice and/or data collection. However, because the 2 groups had equivalent numbers of under- and overtransfusion protocol violations and because there was no difference in hemoglobin levels throughout the study, physician bias toward withholding transfusions in the monitor group seems unlikely. The introduction of bias in the key secondary outcome, namely, phlebotomy loss, also seems improbable, because these determinations were based primarily on the computer records of the 2 hospitals and to a much lesser extent on the research nurses' records.

Second, phlebotomy loss measurements were necessarily estimates based on hospital laboratory testing reports; hematocrit levels of blood samples are highly variable, the volume of blood drawn for individual laboratory tests is operator dependent, and blood loss on bedding and gauze is not taken into account. As a result, phlebotomy data are far less precise than the data for either the volume of RBCs transfused or the number of transfusions. An additional, albeit unlikely, contributor to phlebotomy loss is injury to RBCs sustained as a result of monitor use. However, blood sampling performed with a monitor is as gentle (or more so) than sampling performed manually. The monitor's slow, even withdrawal of blood, its use of isotonic fluid for calibration, and its construction with conventional plastic intravenous tubing almost certainly reduce the risk of RBC injury.

Third, the study included only 2 study centers, making conclusions potentially difficult to generalize to other centers. This may not a serious study limitation because, although our 2 centers differed significantly in laboratory phlebotomy loss, the study's modeled primary outcome results were unaffected. However, the week-long use of UACs at both centers suggests that the results cannot be extrapolated to centers that use UACs but may not leave them in for comparable periods or do not use UACs because they prefer capillary blood testing and/or noninvasive monitoring.

Fourth, the study was underpowered to test for important differences in neonatal mortality, morbidity, and neurodevelopmental outcome rates. This means that we could not assess whether the monitor's slow, even rate of withdrawal (at least 10 times slower than a manual blood draw) would result in more stable cerebral oxygenation,[17] potentially leading to reductions in rates of intraventricular hemorrhage and periventricular leukomalacia, or whether in-line monitoring could reduce rates of nosocomial infections and/or infections among health care providers by circumventing the need to enter the intra-arterial circuit.

Finally, a cost-benefit analysis was not part of the present study. However, in a previous study of infants of similar birth weight that used a hypothetical analytical model that included blood cell transfusions, we demonstrated economic savings with the use of this monitor, even for infants who died within the first 3 days of life.[13]

CONCLUSIONS

Although we overestimated the effect of POC devices in our 2-week study, the observed first-week reductions in both cumulative phlebotomy loss and RBC transfusion volume were impressive, especially given the premature termination of the study and the inexperience of the users in the effective application of this new technology. The principle conclusion reported in this clinical trial, ie, that in-line monitoring reduces RBC transfusions among ELBW infants, is very encouraging. This is the first time that a randomized clinical trial has demonstrated clinically significant reductions in neonatal transfusion number and volume. The fact that the reductions were accomplished by reducing laboratory phlebotomy loss early in life points to this as a major cause of neonatal anemia. Before we can recommend that this technology be adopted in other NICUs, a multicenter study to provide more data from a greater spectrum of centers is needed to confirm our findings. Participants in such a study would need to agree on the application of uniform practices in using the monitor, and the implementation of standardized practices is difficult to achieve in unmasked studies involving medical technologies, because the likelihood of bias resulting from differences in operator behavior cannot be controlled for easily.[18] Given the important results of our investigation, however, we think that such a study should be undertaken because, in the absence of noninvasive laboratory testing, POC devices like the one tested in this study offer the greatest potential for addressing the problem of neonatal anemia in a clinically beneficial way.

Acknowledgments

This study was supported by General Clinical Research Centers Program, National Center for Research Resources, grants RR00059 and RR00070, National Institutes of Health grant P01 HL46925, the Children's Miracle Network Telethon, and Metracor Technologies.

We acknowledge the technical assistance and data-collection contributions of Gretchen Cress, RN, Karen J. Johnson, RN, Natalie W. Connelly, RN, Petra Swidler, MD, Laura McKae, RN, and Siv Modler. The clinical laboratory and nursing personnel at both sites provided essential help with the calibration, operation, and troubleshooting of the monitors. Mark A. Hart provided expert secretarial help, and Michaelanne Widness provided editorial suggestions. Ronald G. Strauss, MD, and William Clark, PhD, provided helpful comments and suggestions on the manuscript.

ABBREVIATIONS

ELBW	extremely low birth weight
RBC	red blood cell
UAC	umbilical artery catheter
POC	point-of-care

REFERENCES

1. Levy GJ, Strauss RG, Hume H, et al. A national survey of neonatal transfusion practices, I: red blood cells. Pediatrics 1993;91:523–529. [PubMed: 8441554]
2. Bifano EM, Curran TR. Minimizing donor blood exposure in the neonatal intensive care unit. Clin Perinatol 1995;22:657–669. [PubMed: 8521687]
3. Maier RF, Sonntag J, Walka MM, Liu G, Obladen M. Changing practices of red blood cell transfusions in infants with birth weights less than 1000 g. J Pediatr 2000;136:220–224. [PubMed: 10657829]
4. Widness JA, Seward VJ, Kromer IJ, Burmeister LF, Bell EF, Strauss RG. Changing patterns of red blood cell transfusion in very low birth weight infants. J Pediatr 1996;129:680–687. [PubMed: 8917234]
5. Widness JA. Pathophysiology, diagnosis and prevention of anemia during the neonatal period. NeoReviews 2000;1:e61–e68.
6. Ohls RK. Erythropoietin treatment in extremely low birth weight infants: blood in versus blood out. J Pediatr 2002;141:3–6. [PubMed: 12091842]
7. Kost GJ, Ehrmeyer SS, Chernow B, et al. The laboratory-clinical interface: point-of-care testing. Chest 1999;115:1140–1154. [PubMed: 10208220]
8. Widness JA, Kulhavy JC, Johnson KJ, et al. Clinical performance of an in-line point-of-care monitor in neonates. Pediatrics 2000;106:497–504. [PubMed: 10969094]
9. Hack M, Horbar JD, Mallow MH, Tyson JE, Wright EC, Wright LL. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. Pediatrics 1991;87:587–597. [PubMed: 2020502]
10. Hack M, Wright LL, Shankaran S, Tyson JE, Horbar JD, Bauer CR. Very-low-birth-weight outcomes of the National Institute of Child Health and Human Development Neonatal Network, November 1989 to October 1990. Am J Obstet Gynecol 1995;172:457–464. [PubMed: 7856670]
11. Fanaroff AA, Wright LL, Stevenson DK, Shankaran S, Donovan EF, Ehrenkranz RA. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, May 1991–December 1992. Am J Obstet Gynecol 1995;173:1423–1431. [PubMed: 7503180]
12. Lin JC, Strauss RG, Kulhavy JC, et al. Phlebotomy overdraw in the neonatal intensive care nursery. Pediatrics 2000;106(2) Available at: www.pediatrics.org/cgi/content/full/106/2/e19.
13. Alves-Dunkerson J, Hilsenrath PE, Cress GA, Widness JA. Cost analysis of a neonatal point-of-care monitor. Am J Clin Pathol 2002;117:809–818. [PubMed: 12090433]
14. Elashoff, JD. nQuery Advisor User's Guide. Dixon Associates; Los Angeles, CA: 1995.

15. Billman GF, Hughes AB, Dudell GG, et al. Bias and precision of an in-line ex vivo point-of-care monitor: a multicenter study. Clin Chem 2002;48:2030–2043. [PubMed: 12406990]

16. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–417. [PubMed: 9971864]

17. Schulz G, Keller E, Haensse D, Arlettaz R, Bucher HU, Fauchere JC. Slow blood sampling from an umbilical artery catheter prevents a decrease in cerebral oxygenation in the preterm newborn. Pediatrics 2003;111(1) Available at: www.pediatrics.org/cgi/content/full/111/1/e73.

18. Bryan AC. The oscillations of HFO. Am J Respir Crit Care Med 2001;163:816–817. [PubMed: 11282749]

19. Stevenson DK, Wright LL, Lemons JA, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. Am J Obstet Gynecol 1998;179:1632–1639. [PubMed: 9855609]

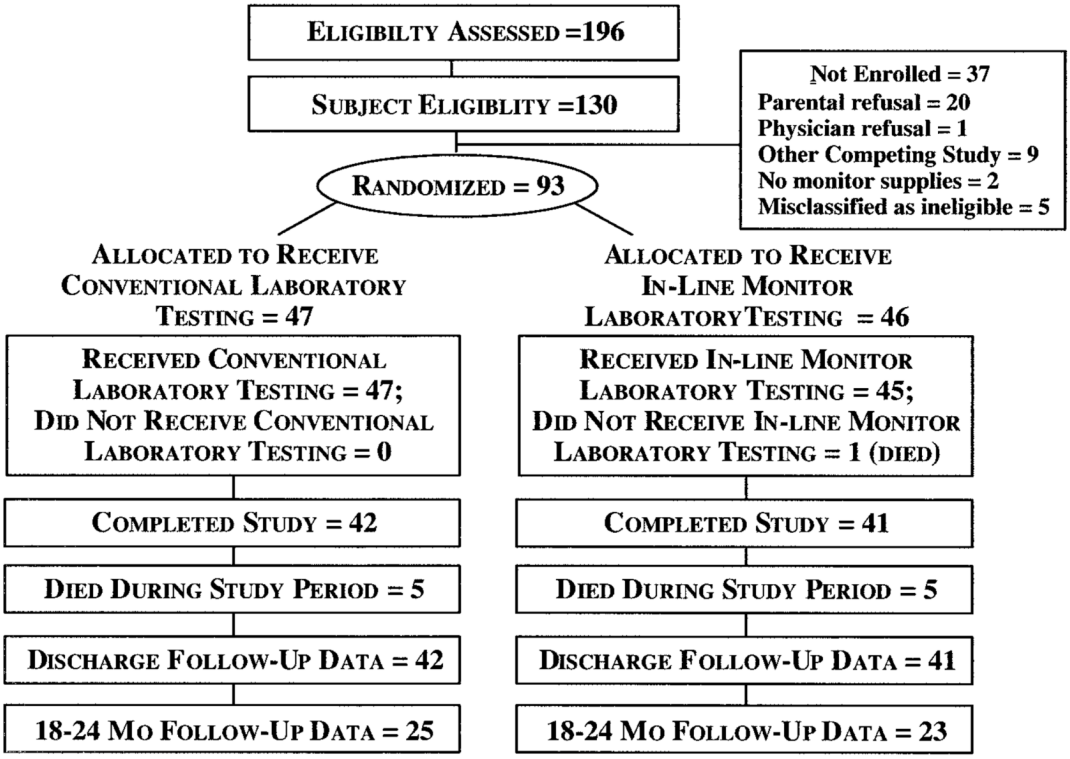

Fig 1.
Flow diagram of study subjects at each stage of the clinical trial.

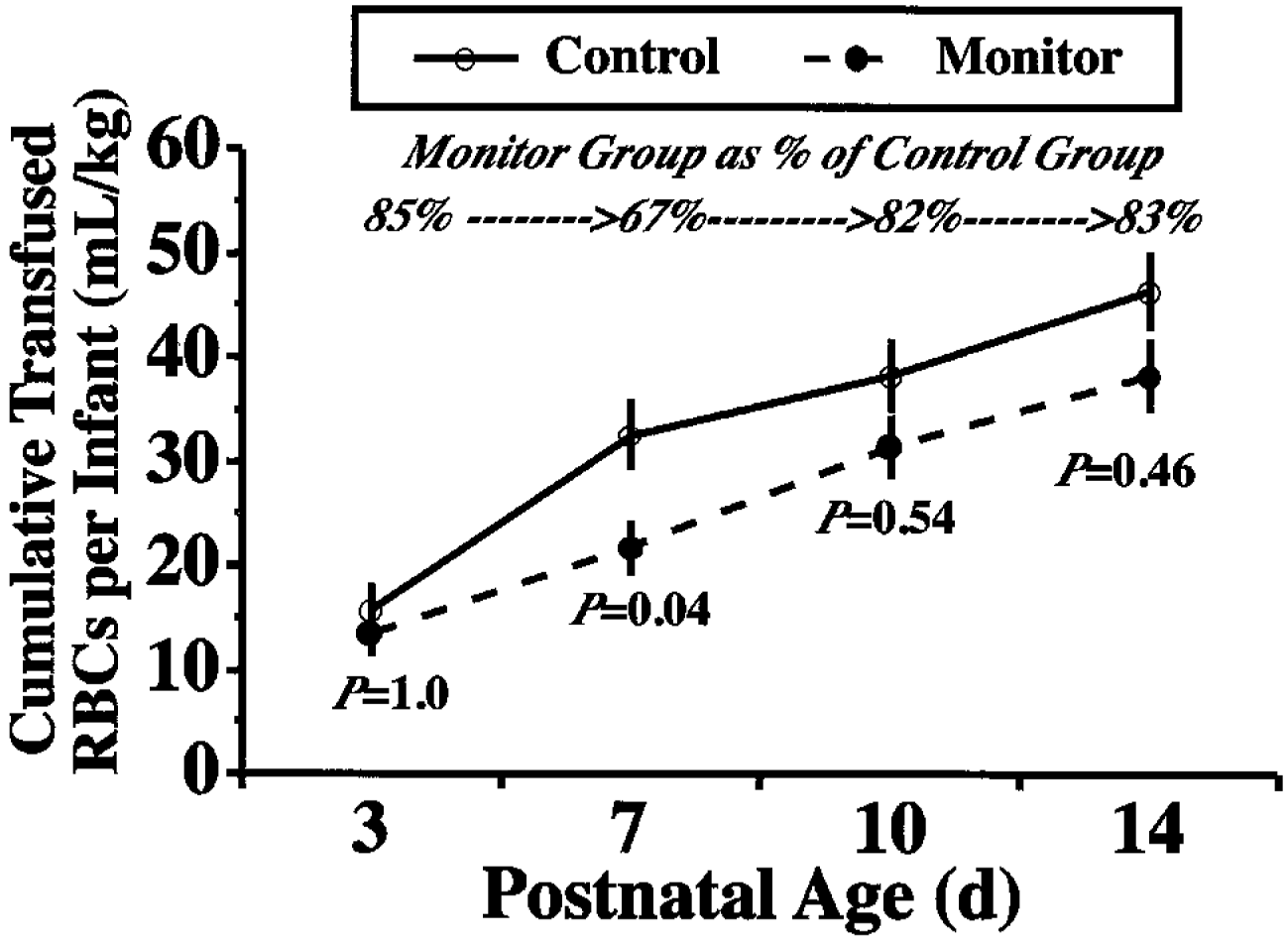

Fig 2.

Results of intention-to-treat analysis for cumulative volume of RBC transfusions according to study group. The error bars represent the SEM. Data shown represent those derived in the linear regression analysis of variance model with adjustment for study site and birth weight stratification. *P* values represent group comparisons at the postnatal ages indicated applying the Bonferroni correction.

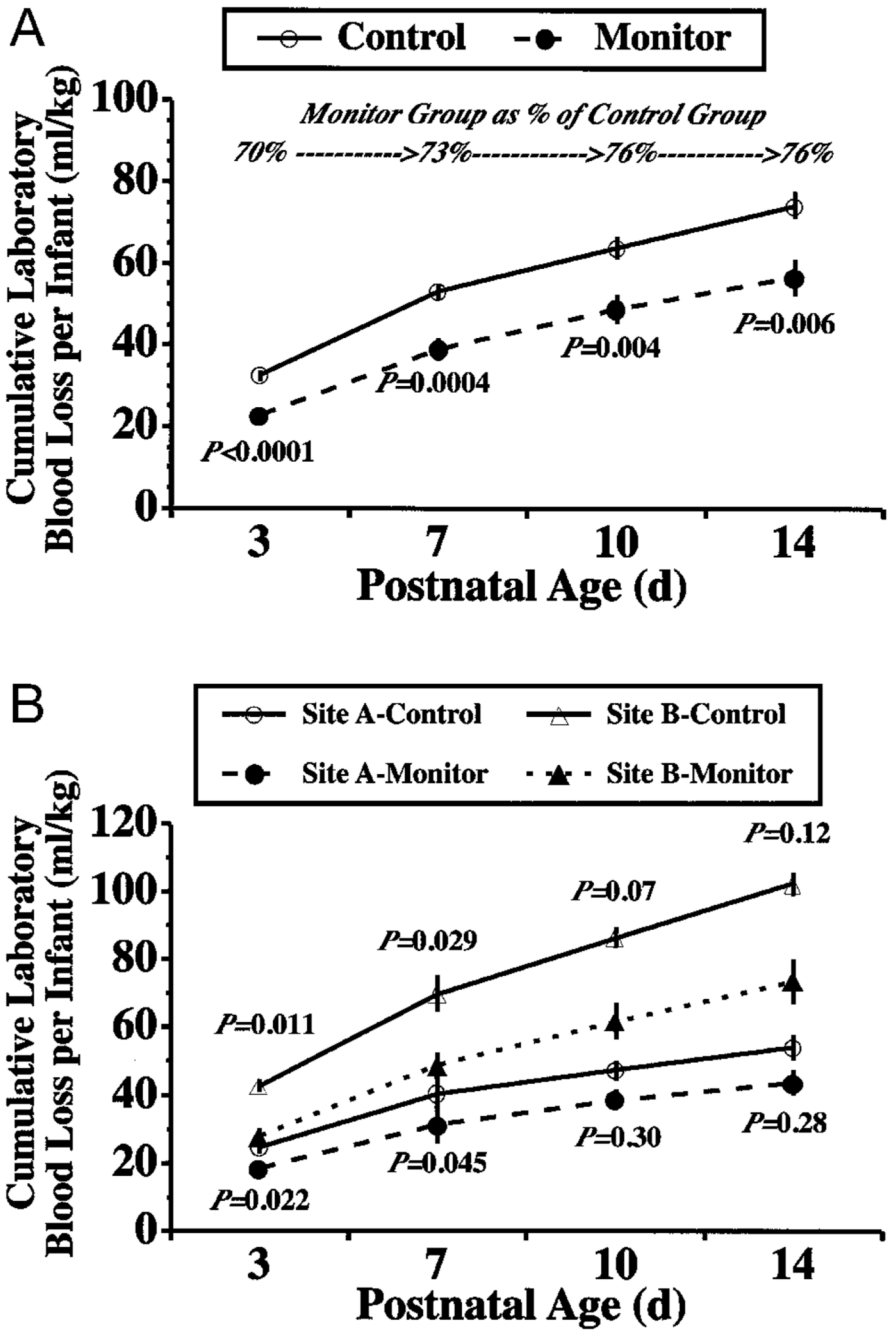

Fig 3.

Results of cumulative laboratory blood loss during the first 2 weeks of life according to study group, for the entire study population (A) and for the 2 study sites (B). The error bars represent the SEM. Data shown represent those derived in the linear regression analysis of variance model with adjustment for study site and birth weight stratification. *P* values represent group (A) or site (B) comparisons at the postnatal ages indicated applying the Bonferroni correction.

TABLE 1

Indications for RBC Transfusions During the 14-Day Study Period

Hematocrit, %*	Clinical Conditions and Circumstances
<40	Ventilation with ≥40% oxygen, sepsis, or necrotizing enterocolitis
<35	Ventilation with <40% oxygen or NCPAP or hood treatment with ≥40% supplemental oxygen
<30	Receiving NCPAP or hood oxygen supplementation of >25% but <40% or receiving 100% oxygen via nasal cannula at a flow rate of ≥0.25 L/min
<30	Major surgical procedures while not receiving respiratory support (with or without supplemental oxygen)

* If not previously ordered because of clinical indications, hematocrit measurements were performed on Monday, Wednesday, and Friday. To warrant administration of a RBC transfusion, 2 hematocrit determinations performed within 24 hours of one another below the hematocrit levels indicated were required. NCPAP indicates nasal continuous positive airway pressure.

TABLE 2

Maternal Data at Study Entry According to Study Group

	Control Group (*n* = 47)	Monitor Group (*n* = 46)	*P* Value
Age, y	27.8 ± 6.7	26.2 ± 7.1	.28
Race/ethnicity, *n* (%)			.92
White	32 (68)	29 (63)	
Black	7 (15)	7 (15)	
Asian	4 (8)	4 (9)	
Hispanic	4 (8)	6 (13)	
Prenatal steroid treatment, *n* (%)*	41 (87)	34 (74)	.12
Tocolysis, *n* (%)	36 (77)	28 (61)	.12
Prepartum antibiotics, *n* (%)	34 (72)	35 (76)	.81
Rupture of membranes ≥24 h, *n* (%)	9 (19)	15 (33)	.16
Cesarean section, *n* (%)	29 (62)	25 (54)	.53

Data are expressed as mean ± SD or as number of subjects (percentage of subjects).

* Includes maternal betamethasone treatment regardless of dose or duration before delivery.[19]

TABLE 3

Neonatal Data at Study Entry According to Study Group

	Control Group (*n* = 47)	Monitor Group (*n* = 46)	*P* Value
Birth weight, g	734 ± 120	742 ± 132	.78
Weight of 500–750 g, *n* (%)	24 (51)	22 (48)	.84
Weight of 751–1000 g, *n* (%)	23 (49)	24 (52)	
Gestational age, wk	26.0 ± 1.8	26.0 ± 2.0	.83
Male, *n* (%)	24 (51)	26 (56)	.68
Inborn, *n* (%)	44 (94)	38 (83)	.12
Multiple birth, *n* (%)	17 (36)	12 (26)	.37
Apgar score of ≤3 at 5 min, *n* (%)	5 (11)	3 (6)	.71
Hemoglobin level, g/L	147 ± 25	143 ± 29.4	.42
Plasma ferritin level, μg/L	142 (69–279) [42]	151 (79–246) [44]	.99

Data are expressed as the mean ± SD, the median (interquartile range), or the number of subjects (percentage of subjects); numbers in brackets are numbers if different from group numbers.

TABLE 4

Laboratory and Clinical Outcomes According to Study Group

	Control Group (*n* = 47)	Monitor Group (*n* = 46)	*P* Value
Duration of UAC use, d	5.8 (4.5–8.7)	6.6 (3.8–10.2)	.57
Laboratory data on day 7			
Hemoglobin, g/L	134 ± 17.4 [44]	135.1 ± 19.3 [43]	.29
Hemoglobin change from day 1, g/L	−7.8 [42]	−7.6 [41]	.98
Laboratory data on day 14			
Hemoglobin, g/L	138 ± 14.8 [42]	131.9 ± 14.4 [41]	.07
Hemoglobin change from day 1, g/L	−9.3 [42]	−10.1 [41]	.83
Plasma ferritin, μg/L	464 (299–605) [38]	489 (274–709) [37]	.78
Ferritin change from day 1, μg/L	283 (126–403) [35]	338 (67–493) [37]	.62
Mechanical ventilation other than CPAP, *n* (%)	44 (94)	43 (94)	.99
Postnatal corticosteroids, *n* (%)	17 (36)	20 (44)	.53
Intraventricular hemorrhage grade III/IV, *n* (%)	7 (15)	8 (17)	.78
Patent ductus arteriosus, *n* (%)	29 (62)	21 (46)	.15
Oxygen treatment at 36 wk, *n* (%)	26/47 (55)	29/46 (63)	.53
Bacteremia during study (≤14 d), *n* (%)	2 (4)	6 (13)	.16
Bacteremia after study (>14 d), *n* (%)	9 (21) [42]	7 (17) [41]	.78
Necrotizing enterocolitis (Bell's stage ≥II), *n* (%)	5 (11)	2 (4)	.43
Threshold retinopathy of prematurity, *n* (%)*	3 (15) [39]	4 (14) [35]	.70
Periventricular leukomalacia, *n* (%)*	2 (5)	0 (0)	.49
Survival without severe morbidity, *n* (%)†	21/41 (51)	15/37 (40)	.37
Age at discharge, d	102 (86–121)	91 (77–124)	.68
Weight at discharge, g	2760 (2260–3300)	2660 (2410–3109)	.84

Data are expressed as the mean ± SD, the median (interquartile range), or the number of subjects (percentage of subjects); numbers in square brackets are numbers if different from group numbers. CPAP indicates continuous positive airway pressure.

*Treated with laser therapy or cryotherapy.

†Without oxygen treatment at 36 weeks, threshold retinopathy of prematurity, bacteremia after 3 days of life, periventricular leukomalacia, pneumothorax, intraventricular hemorrhage (grades III or IV), or necrotizing enterocolitis (Bell's stage ≥II).[19]