Effect of Umbilical Cord Blood Sampling versus Admission Blood Sampling on Requirement of Blood Transfusion in Extremely Preterm Infants: A Randomized Controlled Trial

Haribalakrishna Balasubramanian, MD, DM, MSc[1], Priyanka Malpani, MD[1], Mythily Sindhur, DCH[1], Nandkishor S. Kabra, MD, DNB, DM, MNAMS, MSc[1], Javed Ahmed, MD[1], and Lakshmi Srinivasan, MD, FAAP[2]

Objective To evaluate the effect of blood sampling from the placental end of the umbilical cord compared with initial blood sampling from neonates, on the need for first packed red blood cell transfusion in extremely preterm infants. We hypothesized that cord blood sampling could delay the time to first blood transfusion.

Study design In this single-center, assessor blind, randomized controlled trial, we included extremely low birth weight neonates <28 weeks of gestational age at birth. Five milliliter of blood for initial laboratory investigations was collected either from the placental end of the umbilical cord (study group) or from the neonate upon neonatal intensive care unit admission (control group). Both groups received similar anemia prevention strategies. The primary outcome was the time (in days) to the first packed red blood cell transfusion, and was compared using survival analysis.

Results Eighty neonates were enrolled. The time to first transfusion was significantly delayed in the cord sampling group (30 vs 14 days, hazard ratio: 0.44, [95% CI 0.27-0.72], $P < .001$). Fewer neonates in the cord sampling group were transfused in the first 28 days of life (30% vs 75%, $P < .001$). Overall transfusion requirements and other clinical outcomes were similar in the groups.

Conclusions Initial blood sampling from placental end of umbilical cord, when combined with anemia prevention strategies, significantly prolonged the time to first transfusion and reduced the need for early transfusions among extremely premature neonates. *(J Pediatr 2019;211:39-45)*.

Trial Registration Ctri.nic.in/ (CTRI/2017/04/008320).

Evidence suggests that 85%-90% of extremely low birth weight (ELBW) infants receive a transfusion during their stay in the neonatal intensive care unit (NICU).[1-3] Small circulating blood volume, suboptimal response to endogenous erythropoietin, short life span of red blood cells, repeated phlebotomies, sampling losses from umbilical catheters, and a higher incidence of morbidities such as intraventricular hemorrhage (IVH) and sepsis render this population vulnerable to early and severe anemia.[4] There is emerging evidence that anemia and/or packed red blood cell (PRBC) transfusions in the first weeks of life in extremely preterm infants may be associated with higher risk of retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and mortality.[5-7] This has led to greater scrutiny of the potential risks of transfusions in preterm neonates,[8,9] and identification of strategies that could minimize need for transfusions such as delayed cord clamping, standardizing transfusion thresholds, and minimizing blood sampling from the neonate.

Phlebotomies in the NICU significantly contribute to blood volume losses in extremely preterm neonates.[10] Blood sampling on admission to the NICU usually involves withdrawal of 4-5 mL of blood and accounts for 30%-40% of the sampling losses occurring over the first postnatal week.[11] Blood samples drawn from the placental end of the umbilical cord at birth can be used to carry out investigations in place of routine admission blood samples collected from neonates. Comparative studies have demonstrated good agreement between the values obtained from cord blood analysis and neonatal venous blood for common

ABS	Admission blood sampling
CBS	Cord blood sampling
ELBW	Extremely low birth weight
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
NEC	Necrotizing enterocolitis
PRBC	Packed red blood cell
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

From the [1]Surya Hospital, Mumbai, Maharashtra, India; and [2]The Children's Hospital of Philadelphia and The University of Pennsylvania, Philadelphia, PA

The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2019.04.033

investigations such as complete blood count, blood typing, blood gases, and sepsis screen.[12,13] This practice has been shown to reduce vasopressor use and the need for early PRBC transfusions in very low birth weight (VLBW) infants.[14]

Placental transfusion strategies (delayed cord clamping, umbilical cord milking) and erythropoietin have independently been shown to reduce the need of PRBC transfusions in very preterm neonates.[15-17] We instituted a neonatal anemia prevention care bundle in our unit specifically targeting extremely preterm neonates. This included a combination of cut umbilical cord milking, regular subcutaneous erythropoietin administration after the first week of age, and minimizing phlebotomy losses. Although we achieved a modest reduction in the overall transfusion rate in the unit, transfusions in the early neonatal period could not be avoided.

We planned to examine the impact of incorporating cord blood sampling into our preexisting anemia prevention bundle, on requirements of early transfusions in extremely preterm neonates. We hypothesized that umbilical cord (placental end) blood sampling in the delivery room (cord blood sampling [CBS]), when compared with blood sampling from the neonate after admission to the NICU (admission blood sampling [ABS]) could delay the time to first blood transfusion and reduce the need for early neonatal PRBC transfusions. Therefore, we conducted this randomized controlled trial to compare the effect of CBS with ABS on transfusion requirements of extremely preterm neonates.

Methods

Trial Design and Settings

The study was a single center, assessor blind, randomized controlled trial with parallel enrollment conducted at the level III NICU of Surya Hospital, Mumbai, Western India. The hospital is part of the Indian National Neonatal Collaborative and contributes data on 120 extremely preterm neonates every year.

The study was approved by the Institutional Ethics Committee and the trial was prospectively registered with Clinical Trial Registry of India (CTRI/2017/04/008320). Written informed consent was obtained from one of the parents or relatives prior to inclusion into the study.

As part of project feasibility assessment, 2 neonatal fellows and staff nurses were trained over a 1-month period in collection of umbilical venous blood from the segment of cord that is discarded after delivery. Study information was disseminated to all the neonatologists and nurses through poster cards.

Eligibility Criteria

Extremely preterm neonates born <28 weeks of gestational age and with birth weight <1000 g were eligible for enrollment. The neonates were either inborn or transferred from maternity hospitals within a 2-km radius of the study center. Outborn infants were considered for enrollment only when our neonatal team could attend the delivery and expedite the transfer within 30 minutes of birth.

Study exclusion criteria were chorioamnionitis, monochorionic twins or triplets, anomalies of the cord (true/false knots, strictures, funisitis of the cord), major congenital anomalies (such as gastroschisis, exomphalos), Rh isoimmunization, or placental abnormalities (such as placenta accreta, marginal insertion, battledore placenta, velamentous insertion).

Study Procedures Prior to and during Delivery

The study team approached mothers admitted to the hospital for an impending delivery prior to 28 weeks to explain the study interventions and elicit their interest in study participation if cord blood collection was successful.

Obstetricians were briefed about the study by the attending neonatologist prior to delivery. Neonates were held at the level of the uterus following vaginal delivery, and on the thighs of the mother following cesarean delivery while the umbilical cord was cut and clamped. The cord was cut at approximately 25 cm of length from the umbilical stump immediately after birth. The neonate was then handed over for stabilization and umbilical cord milking by the neonatal team.

The obstetrician placed the placenta in a sterile basin with the umbilical cord clamped. The placental end of the cord was used for cord blood sampling. The umbilical vein at its insertion on the placenta was prepped with povidone iodine. A sterile 18-gauge needle attached to a 10-mL syringe was used to withdraw 5 mL of blood from the umbilical vein for initial blood investigations and the appropriate laboratory tubes and culture bottles were filled.

A standardized cord milking procedure was performed on all extremely preterm neonates where the umbilical cord was raised and milked 4 times from the cut end by the residents at the rate of 20 cm/2 seconds and then clamped 2-3 cm from the umbilical stump.

Randomization and Blinding following Delivery

If cord sampling was successful and the weight at birth was less than 1000 g, neonates were considered eligible for study enrollment. Written informed consent for the study was obtained from the parents/relatives. Random sequences with varying block sizes were generated by a statistician who was not part of the study. Allocation concealment was performed using sequentially numbered opaque sealed envelopes. Multiple gestation births were independently randomized to the study arms.

Because of the nature of the study, it was not feasible to blind the clinicians performing the sampling technique. However, the outcome assessors (laboratory technicians, primary investigators) were blinded to the intervention.

Study Procedures Postdelivery

In the CBS group, cord blood samples were dispatched to the laboratory in ice packs within 10 minutes of collection. No further samples were collected from the neonate in the

first 12 hours, unless the samples were clotted or the clinical condition warranted earlier testing. In the ABS group, cord blood samples were discarded, and 5 mL of umbilical venous/arterial blood was collected within the first hour of life.

Blood tests performed at birth in either group included (1) Complete blood count (0.5 mL); (2) Blood grouping and cross matching (1 mL); (3) Blood culture (1 mL); (4) Arterial/venous blood gas (0.2 mL); (5) Coagulation profile (1 mL); (6) C-reactive protein (0.4 mL): and (7) G6PD quantitative screen (0.4 mL). Baseline maternal and neonatal data were entered in a predesigned study proforma.

Standard Clinical Care in the NICU

Phlebotomy losses were recorded in the nursing chart on a daily basis. Standard procedures were followed in all infants to minimize unmeasurable blood loss following heel pricks, venipuncture, and umbilical arterial sampling.

Standard laboratory testing included complete blood counts checked twice weekly in the first 2 weeks followed by once weekly for the duration of NICU stay. Central/peripheral venous or arterial samples were collected. Besides the predetermined testing times, additional testing of hemoglobin level was ordered when clinically indicated. Blood gases, sepsis screening, and cultures were carried out as per standard NICU protocols. Routine cranial ultrasounds were performed on day 3, day 7, and day 28 in all the study neonates. Infants diagnosed with IVH grade II or more had twice weekly cranial ultrasounds in the first month.

The transfusion criteria for extremely premature infants in this study were in accordance with the liberal transfusion threshold described in the Premature Infants in Need of Transfusion Study and were stratified by postnatal age and need for respiratory support.[1] Infants on respiratory support were transfused if the hemoglobin level was <12.2 g/dL and 11 g/dL during the first and second postnatal week respectively, and <9 g/dL after the second week of postnatal age. When transfusion criteria were met, PRBCs were administered within a 6-hour time frame. An aliquot of 20 mL/kg of packed RBC (with a measured hematocrit of 70%) was transfused over 4 hours.

In the presence of a concomitant morbidity such as shock, sepsis, IVH (grade III or higher), or concerns over worsening respiratory failure (increase in fraction of inspired oxygen [FiO_2] by 20%, escalation from continuous positive airway pressure to mechanical ventilation, increasing frequency of apnea), transfusion was guided by the clinician's decision. Such deviations from the standard transfusion protocol were documented for all study patients.

As per unit policy, recombinant erythropoietin (300 IU/kg/dose) was administered twice weekly as subcutaneous injections to all ELBW neonates <28 weeks of gestation for a duration of 8 weeks. Elemental iron supplements (4 mg/kg/day) were administered to all preterm neonates after 2 weeks postnatal age or after attainment of full enteral feeds, whichever was later.

Sample Size

Baseline data from our unit demonstrated that ELBW neonates subjected to admission blood sampling received the first PRBC transfusion at a mean postnatal age of 14 days. To postpone the requirement of first blood transfusion by 7 days in CBS group with an assumed SD of 10 days, a sample size of 38 neonates in each group was estimated for a study power of 90% and 2-tailed alpha of 0.05.

Outcomes

The primary outcome of interest was the time (in days) from birth to requirement of the first PRBC transfusion. The other outcomes that were assessed were the need for transfusion by 28 days of age and at discharge, number of transfusions, mean hemoglobin levels at 4 and 6 weeks of postnatal age and at discharge, mortality before discharge, duration of respiratory support and hospital stay and incidence of prematurity related morbidities such as IVH (grade III or more), definite NEC (Bell stage 2 or more), ROP requiring intervention, patent ductus arteriosus needing medical/surgical treatment, periventricular leukomalacia, and bronchopulmonary dysplasia (need for supplemental oxygen or respiratory support by 36 weeks postmenstrual age).

Statistical Analyses

Stata version 13.1(Stata-Corp LP, College Station, Texas) was used for statistical analysis. Descriptive statistics were used to define the variables in both groups. Continuous outcomes in both groups were compared using the 2-sample *t* test or Wilcoxon rank-sum test as appropriate. Categorical variables were evaluated using the Fisher exact test. Analysis was performed using the intention to treat principle. All *P* values were 2 sided, and a value of $P < .05$ was considered statistically significant. The primary outcome was compared using survival analysis. Kaplan Meier survival curves and log-rank tests were used to compare the conditional probabilities of needing the first PRBC transfusion in both groups at regular time intervals throughout the hospital stay. The survival times were censored for neonates who did not require a transfusion until discharge or transfer and for those who died prior to the first PRBC transfusion. Hazard ratios and 95% CIs were calculated. Line plots were constructed to compare weekly hemoglobin values between the 2 groups. Mixed-effects model with postnatal week as fixed effect and patients as random effect, was used to account for within-patient correlation of repeatedly measured hemoglobin values and individual patient related variance in hemoglobin in both groups. Differential effect of treatment group by postnatal week was assessed using an interaction term in the model.

Results

A total of 80 neonates (40 in each group) were enrolled during the study period (April 15, 2017 to August 30, 2018). Cut umbilical cord milking was performed per standard protocol in all neonates. After randomization to CBS, cord blood

Table I. Baseline characteristics

Characteristics	CBS (n = 40)	ABS (n = 40)
Maternal characteristics		
Maternal age (y)	30.5 ± 6.6	33.4 ± 4.56
Pregnancy induced hypertension	12 (30%)	13 (32%)
Gestational diabetes mellitus	6 (15%)	10 (25%)
Anemia	17 (42%)	13 (32%)
Antepartum hemorrhage	9 (22%)	6 (15%)
Premature rupture of membranes >24 h	16 (40%)	18 (45%)
Cesarean delivery	30 (75%)	33 (82%)
Any antenatal steroid	39 (97%)	39 (97%)
Complete antenatal steroid	33 (82%)	27 (67%)
Neonatal characteristics		
Gestational age (wk)	26.5 ± 1.25	26.4 ± 1.39
Gestational age <26 wk	14 (35%)	14 (35%)
Outborn	11 (27%)	13 (32%)
Male sex	19 (47%)	20 (50%)
Birth weight (g)	825 ± 141.6	808 ± 142.5
Birth weight <750 g	14 (35%)	14 (35%)
Small for gestational age	12 (30%)	16 (40%)
Multiple pregnancy	16 (40%)	25 (62%)
Requirement of resuscitation	28 (70%)	28 (70%)
Umbilical arterial line	20 (50%)	18 (45%)

Data expressed as n (%) or mean ± SD.

samples of 3 patients were clotted. Only blood cultures could be processed from fetal blood in these patients. Samples were obtained from these infants for blood grouping, complete blood count, and blood gas within 12 hours of birth. Admission blood samples were accidentally drawn in 1 neonate enrolled in the CBS group. The study enrollment process is depicted in **Figure 1** (available at www.jpeds.com).

Maternal and neonatal demographic characteristics were similar in both groups (**Table I**). The mean gestational age and birth weights of study subjects was 26.4 weeks and 815 g. At least 1 dose of antenatal steroid was administered in 97% of mothers, 79% of infants were delivered via cesarean delivery, and 70% of the neonates needed resuscitation at birth.

All 80 neonates were included in the survival analysis for the primary outcome. Four infants had died during the NICU stay of which one did not receive PRBC transfusion. IVH (grade 3) was the cause of death in 3 patients. None of the 4 patients who were transferred received PRBC during hospital stay.

The median time to the first transfusion was 30 days in the CBS group and 14 days in the ABS group. Kaplan Meier survival curves demonstrate that the probability of needing a transfusion in the cord sampling group was 56% lower than the admission sampling group throughout the NICU stay (hazard ratio = 0.44, 95% CI 0.27-0.72, log-rank *P* value ≤ .001) (**Figure 2**). Cox proportional hazards regression model was used to adjust for covariates that were significant on univariate analysis (gestational age, outborn deliveries, incidence of gastro intestinal bleed, and baseline hemoglobin). The unadjusted and adjusted hazard ratios were consistent with the primary analyses. Death was infrequent in both groups and, hence, was not included as a competing risk event in the Cox model. There was no significant difference in the overall transfusion rate during NICU stay, however, very few neonates in the CBS group

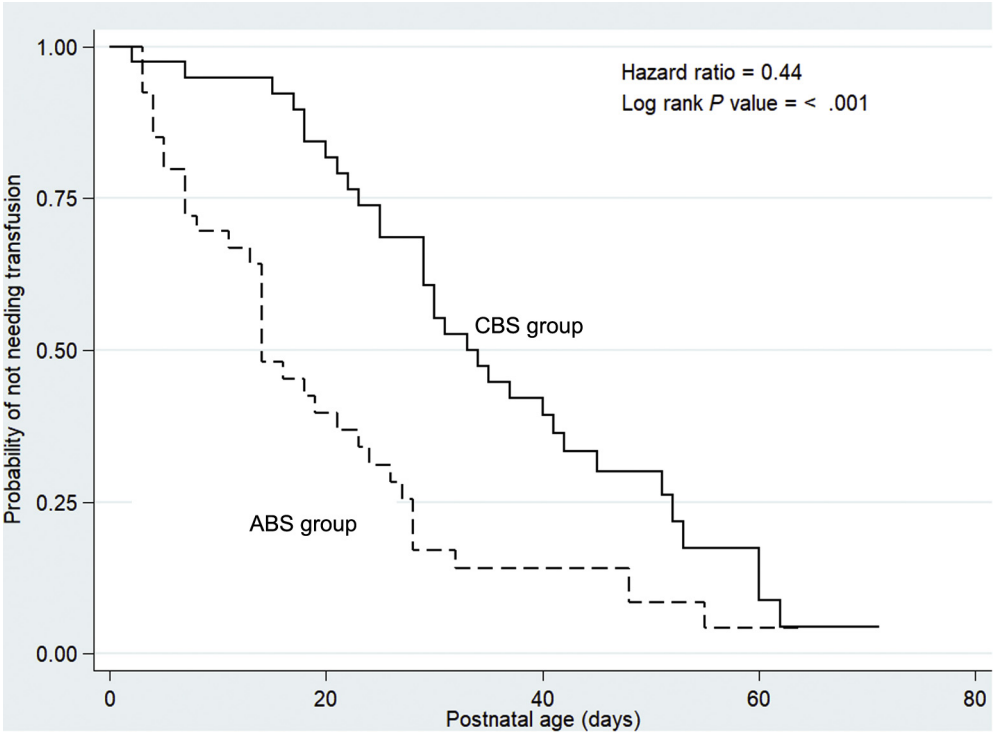

Figure 2. Comparison of PRBC requirements during NICU stay.

Table II. Hematologic outcomes

Outcomes	CBS, n = 40	ABS, n = 40	Relative risk or mean/median difference (95% CI)	*P* value
PRBC during NICU stay	32 (80%)	35 (87%)	0.91 (0.75-1.11)	.54
Time to first blood transfusion	30 (21-41)	14 (7-26)	15 (9-22)	<.001
PRBC within first 2 wk	2 (5%)	20 (50%)	0.1 (0.04-0.27)	<.001
PRBC within first 4 wk	12 (30%)	30 (75%)	0.4 (0.25-0.63)	<.001
Need for one or more PRBC	2 (5%)	5 (12%)	0.4 (0.09-1.83)	.432
Number of PRBC transfusions	1	1		1.00
Volume of PRBC transfused (mL)	21 (12-29)	18 (15-30)	0 (−7, 5)	.97
Baseline hemoglobin (g/dL)*	15.2 ± 2.2	15.7 ± 1.7	−0.53 (−1.42, 0.36)	.24
Transfusion hemoglobin (g/dL)	9.0 ± 0.8	9.6 ± 0.8	−0.56 (−0.88, −0.07)	.02
Transfusion guided by hemoglobin threshold†	30 (95%)	32 (92%)	1.02 (0.89-1.17)	1.00
Discharge hemoglobin (g/dL)	11.3 ± 1.47	11.5 ± 1.29	−0.20 (−0.86, 0.45)	.54
Need for platelet transfusion	5 (12%)	6 (15%)	0.83 (0.27-2.52)	1.00

Data expressed as n (%), mean ± SD, or median (25th quartile- 75th quartile).
*Cord blood analysis was successful in 37/40 infants in the CBS group.
†32 infants in CBS group and 35 infants in ABS group received PRBC transfusion.

received PRBC transfusions in the first 4 weeks of age (**Table II**).

We observed a separation in the mean hemoglobin values between the 2 groups in the first few postnatal weeks (**Figure 3**; available at www.jpeds.com). These findings were corroborated by the mixed model analysis, that suggested a decline in the hemoglobin levels with postnatal age, and significantly lower hemoglobin values in the ABS group compared with the CBS group in the first 2 weeks of postnatal age (*P* value for time-by-treatment group interaction of <.001), after accounting for patient related random effects. Neonatal outcomes were similar in both groups (**Table III**).

Discussion

Our study demonstrates that sampling from the placental segment of the umbilical cord rather than from the neonate, significantly prolonged the time from birth to first PRBC transfusion and reduced the need for transfusions in the neonatal period (first 4 weeks of life) in extremely preterm neonates. A trend toward reduced incidence of ROP needing treatment was also noted in the cord sampling group (32% vs 57%).

The strength of our study is the randomized control design with robust methodology and selection of a population that is most likely to benefit from minimization of early postnatal blood loss.

The burden of transfusion among extreme preterm infants is high. An Australian population based study of 5326 neonates transfused between 2001 and 2011 reported that 4% of preterm neonates >28 weeks received an RBC transfusion before 28 days of life, compared with 60% of those born <28 weeks.[18] Prevention of anemia and limiting transfusions in the first month of age could have greater clinical significance in preterm neonates. Anemia during the first week of life in extremely preterm neonates was identified as an independent risk factor for ROP warranting treatment.[5] In a cohort of 1077

Table III. Neonatal outcomes

Outcomes	CBS group	ABS group	Relative risk or mean/median difference (95% CI)	*P* value
Death	2/40 (5%)	2/40 (5%)	1	1.00
Early onset sepsis	6/40 (15%)	4/40 (10%)	1.5 (0.46-4.9)	.74
IVH (grade III or more)	1/40 (2.5%)	2/40 (5%)	0.5 (0.05-5.1)	1.00
Patent ductus arteriosus requiring treatment	25/40 (62%)	23/40 (57%)	1.09 (0.76-1.56)	.82
Definite NEC	1/37 (3%)	2/35 (6%)	0.47 (0.04-4.99)	.61
ROP requiring treatment	12/37 (32%)	20/35 (57%)	0.57 (0.33-0.96)	.057
Late onset sepsis	10/37 (27%)	10/35 (28%)	0.94 (0.45-2.00)	1.00
Chronic lung disease	15/37 (40%)	17/35 (48%)	0.83 (0.50-1.40)	.64
Pulmonary hemorrhage	1/40 (2.5%)	2/40 (5%)	0.5 (0.05-5.3)	1.00
Gastrointestinal bleed	4/40 (10%)	6/40 (15%)	0.67 (0.2-2.18)	.74
Need for ventilation	31/40 (77%)	34/40 (85%)	0.91 (0.74-1.13)	.57
Ventilation, d	6 (5-10)	7 (4-10)	0 (−3, 2)	.98
Need for CPAP	35/40 (87%)	34/40 (85%)	1.03 (0.86-1.23)	1.00
CPAP, d	31 (16-56)	34 (15-59)	1 (−11, 13)	.98
Umbilical arterial line, d	3 (2-5)	4 (3-5)	−1 (−2, 0)	.22
Time of initiation of feed, d	3.5 (2-5)	4 (3-5)	0 (−1, 1)	.44
Time for full feed, d	9 (7-11)	11 (8-15)	−1 (−3, 1)	.27
Duration of hospital stay, d	64 (50-85)	70 (54-93)	−8 (−22, 6)	.24

CPAP, continuous positive airway pressure.
Data expressed as n/N (%), median (25th- 75th quartile).

VLBW infants, PRBC transfusion in the first 28 days of life was associated with an increased risk of in hospital mortality.[6] A drop in the nadir of hemoglobin by 1 g/dL in the neonatal period was reported to increase the risk of NEC by 65% in VLBW infants.[7] A retrospective study showed that 12% of transfusions in VLBW infants were followed by a 5 mg/dL increase in serum bilirubin levels.[19] Transfusion associated immunologic and hemolytic reactions, although rare in neonates, could be potentially fatal in this vulnerable population.

Clinical trials on PRBC transfusions for extremely preterm neonates conducted in the past decade have reported a median time of 4 days to the first transfusion, irrespective of the transfusion threshold.[1,2] Those neonates also received an average of 4-5 transfusions during NICU stay. Although definitive evidence is still awaited regarding the best approach to transfusion thresholds, we used a liberal transfusion threshold for our study based on evidence suggesting that there may be potential benefits for long term neurocognitive outcomes in ELBW neonates.[20] It was reassuring to note the marked reduction in early PRBC transfusions in CBS group despite using a high hemoglobin threshold to initiate transfusion.

Baer et al compared 91 VLBW neonates with admission blood samples drawn from the discarded umbilical cord with matched controls.[14] Infants who had admission blood samples obtained by CBS had significantly higher hemoglobin levels (at least 1 g % higher) at 12-24 hours of life and required fewer RBC transfusions in the first week of life (25% vs 64%) compared with controls. The effect was consistent even in infants that did not receive a placental transfusion. Our study conducted in a higher risk population demonstrated a pronounced and extended effect (4 weeks of age) of CBS in avoiding transfusion when combined with anemia prevention strategies.

The benefits of combining anemia prevention strategies have previously been reported. As part of a quality improvement project, neonatal units that employed a combination of anemia prevention strategies (darbepoetin therapy, umbilical cord milking, and use of cord blood for admission laboratory studies) had lower RBC transfusion rates.[21] Pharmacodynamically optimized erythropoietin treatment combined with 55% reduction in phlebotomy losses predicted marked reductions in PRBC requirements among VLBW neonates.[22]

The anemia prevention bundle followed in our NICU was instrumental in reducing the median number of transfusions to 1 in both groups. Our trial demonstrates that implementation of CBS in addition to the anemia bundle, provides an added benefit, by significantly reducing the need of transfusion in the first month of life in extremely preterm infants.

Our major limitation was the small sample size and, hence, the inability to determine the impact of our intervention on neonatal morbidities and long-term neurodevelopment. Use of a restrictive instead of a liberal transfusion threshold could have further reduced the transfusion requirements in both groups. Delayed cord clamping was not performed in the study patients as at least 80% of them were expected to need immediate resuscitation. Cord milking was performed on all patients, however, repeated milking of the cut, rather than an intact umbilical cord was also a limitation of our study. The results of this study may not be generalizable to less sick or older preterm infants, who may need less blood sampling for laboratory tests upon admission. It was also not possible to quantify gastric and pulmonary blood losses, although they occurred only in a minority of patients.

Adherence to the transfusion protocols in 95% of the study patients reduced the potential for performance bias in our study. The higher mean hemoglobin at transfusion in the ABS group is consistent with the fact that a greater proportion of neonates in that group were transfused in the first 2 weeks when the threshold for transfusion was high.

Adopting this intervention in routine clinical practice is not without challenges. The need for a person trained in cord sampling during delivery, logistics of obtaining 5 mL blood from the cord, and processing delays especially in outborn neonates are important considerations. Caroll et al reported unsuccessful cord sampling in 13% and clotted cord samples in 9.3% of their extreme preterm cohort.[23] As our enrollment flow diagram demonstrates, we experienced similar challenges in a proportion of the eligible population of preterm infants. Randomization of infants prior to cord sampling could have led to a more realistic assessment of our intervention in routine practice. However, we chose to randomize infants after cord blood collection because failed attempts at cord sampling were perceived to compromise the treatment fidelity between the 2 groups, especially with small sample sizes.

In summary, our randomized trial demonstrates that initial blood sampling from the placental end of umbilical cord, when combined with anemia prevention strategies, significantly prolongs the time to first transfusion and reduces the need for transfusions in the neonatal period. Additional studies with adequate power are required to quantify the impact of this intervention on outcomes of preterm infants. ■

Submitted for publication Jan 17, 2019; last revision received Apr 12, 2019; accepted Apr 16, 2019.

Reprint requests: Haribalakrishna Balasubramanian, MD, DM, MSc, Surya Hospital, SV Rd, Santacruz West, Mumbai, Maharashtra, India 400054. E-mail: drhari@suryahospitals.com

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006;149:301-7.
2. Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics 2005;115:1685-91.
3. 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;129:680-7.

4. Colombatti R, Sainati L, Trevisanuto D. Anemia and transfusion in the neonate. Semin Fetal Neonatal Med 2016;21:2-9.
5. Lundgren P, Athikarisamy SE, Patole S, Lam GC, Smith LE, Simmer K. Duration of anaemia during the first week of life is an independent risk factor for retinopathy of prematurity. Acta Paediatr 2018;107:759-66.
6. dos Santos AM, Guinsburg R, de Almeida MF, Procianoy RS, Leone CR, Marba ST, et al. Red blood cell transfusions are independently associated with intra-hospital mortality in very low birth weight preterm infants. J Pediatr 2011;159:371-6.e1-e3.
7. Patel RM, Knezevic A, Shenvi N, Hinkes M, Keene S, Roback JD, et al. Association of red blood cell transfusion, anemia, and necrotizing enterocolitis in very low-birth-weight infants. JAMA 2016;315:889-97.
8. Christensen RD, Del Vecchio A, Ilstrup SJ. More clearly defining the risks of erythrocyte transfusion in the NICU. J Matern Fetal Neonatal Med 2012;25:90-2.
9. Mohamed A, Shah PS. Transfusion associated necrotizing enterocolitis: a meta-analysis of observational data. Pediatrics 2012;129:529-40.
10. Carroll PD, Widness JA. Nonpharmacological, blood conservation techniques for preventing neonatal anemia—effective and promising strategies for reducing transfusion. Semin Perinatol 2012;36:232-43.
11. Christensen RD, Lambert DK, Baer VL, Montgomery DP, Barney CK, Coulter DM, et al. Postponing or eliminating red blood cell transfusions of very low birth weight neonates by obtaining all baseline laboratory blood tests from otherwise discarded fetal blood in the placenta. Transfusion 2011;51:253-8.
12. Beeram MR, Loughran C, Cipriani C, Govande V. Utilization of umbilical cord blood for the evaluation of group B streptococcal sepsis screening. Clin Pediatr 2012;51:447-53.
13. Rotshenker-Olshinka K, Shinwell ES, Juster-Reicher A, Rosin I, Flidel-Rimon O. Comparison of hematologic indices and markers of infection in umbilical cord and neonatal blood. J Matern Fetal Neonatal Med 2014;27:625-8.
14. Baer VL, Lambert DK, Carroll PD, Gerday E, Christensen RD. Using umbilical cord blood for the initial blood tests of VLBW neonates results in higher hemoglobin and fewer RBC transfusions. J Perinatol 2013;33:363-5.
15. Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: a systematic review and meta-analysis. JAMA Pediatr 2015;169:18-25.
16. Ohlsson A, Aher SM. Early erythropoiesis-stimulating agents in preterm or low birth weight infants. Cochrane Database Syst Rev 2017CD004863.
17. Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. Am J Obstet Gynecol 2018;218:1-18.
18. Bowen JR, Patterson JA, Roberts CL, Isbister JP, Irving DO, Ford JB. Red cell and platelet transfusions in neonates: a population-based study. Arch Dis Child Fetal Neonatal Ed 2015;100:F411-5.
19. Christensen RD, Baer VL, Snow GL, Butler A, Ilstrup SJ. Association of neonatal red blood cell transfusion with increase in serum bilirubin. Transfusion 2014;54:3068-74.
20. Whyte RK, Kirpalani H, Asztalos EV, Andersen C, Blajchman M, Heddle N, et al. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 2009;123:207-13.
21. Henry E, Christensen RD, Sheffield MJ, Eggert LD, Carroll PD, Minton SD, et al. Why do four NICUs using identical RBC transfusion guidelines have different gestational age-adjusted RBC transfusion rates? J Perinatol 2015;35:132-6.
22. Rosebraugh MR, Widness JA, Nalbant D, Cress G, Veng-Pedersen P. Pharmacodynamically optimized erythropoietin treatment combined with phlebotomy reduction predicted to eliminate blood transfusions in selected preterm infants. Pediatric Res 2014;75:336-42.
23. Carroll PD, Nankervis CA, Iams J, Kelleher K. Umbilical cord blood as a replacement source for admission complete blood count in premature infants. J Perinatol 2012;32:97-102.

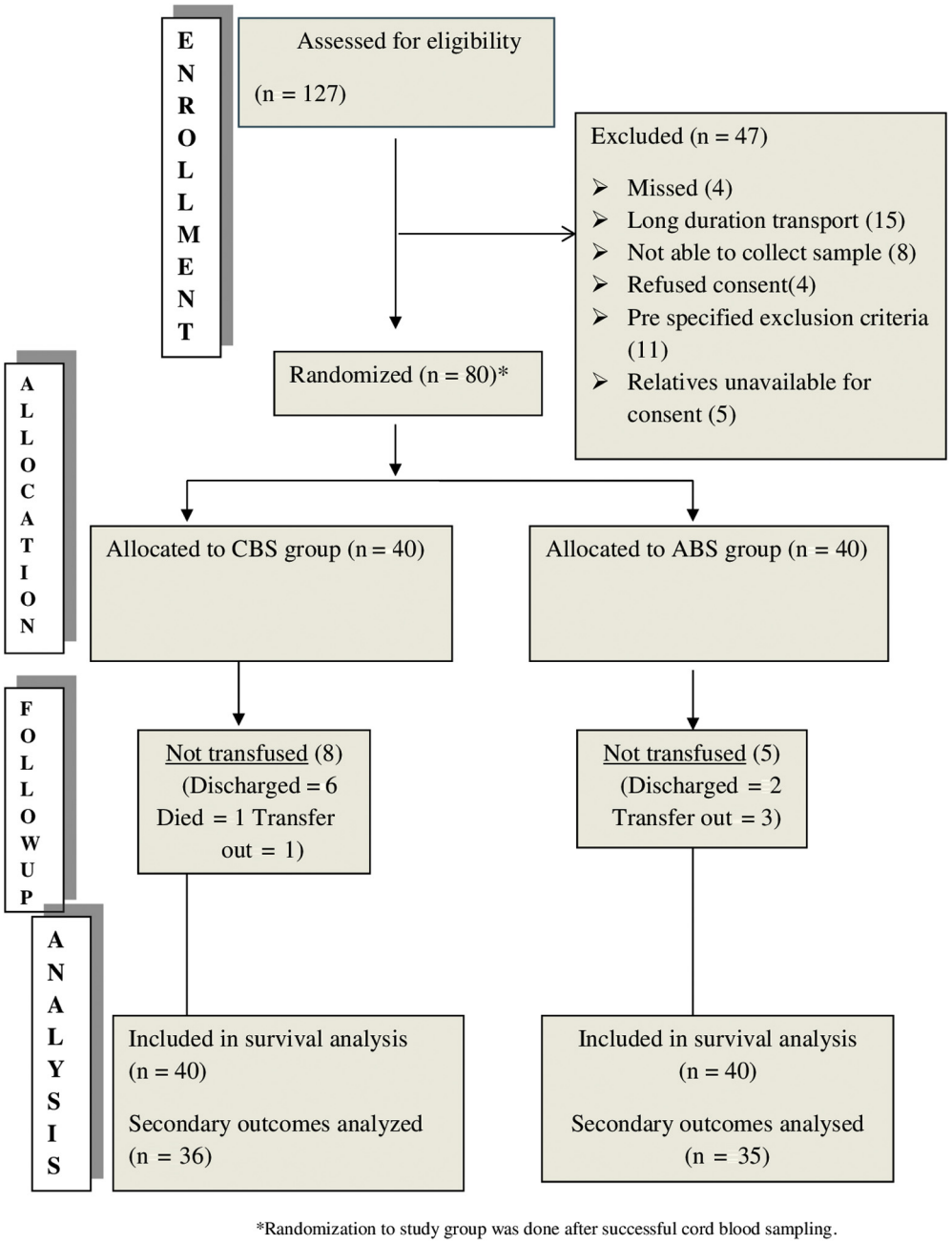

Figure 1. Flowchart of study enrollment.

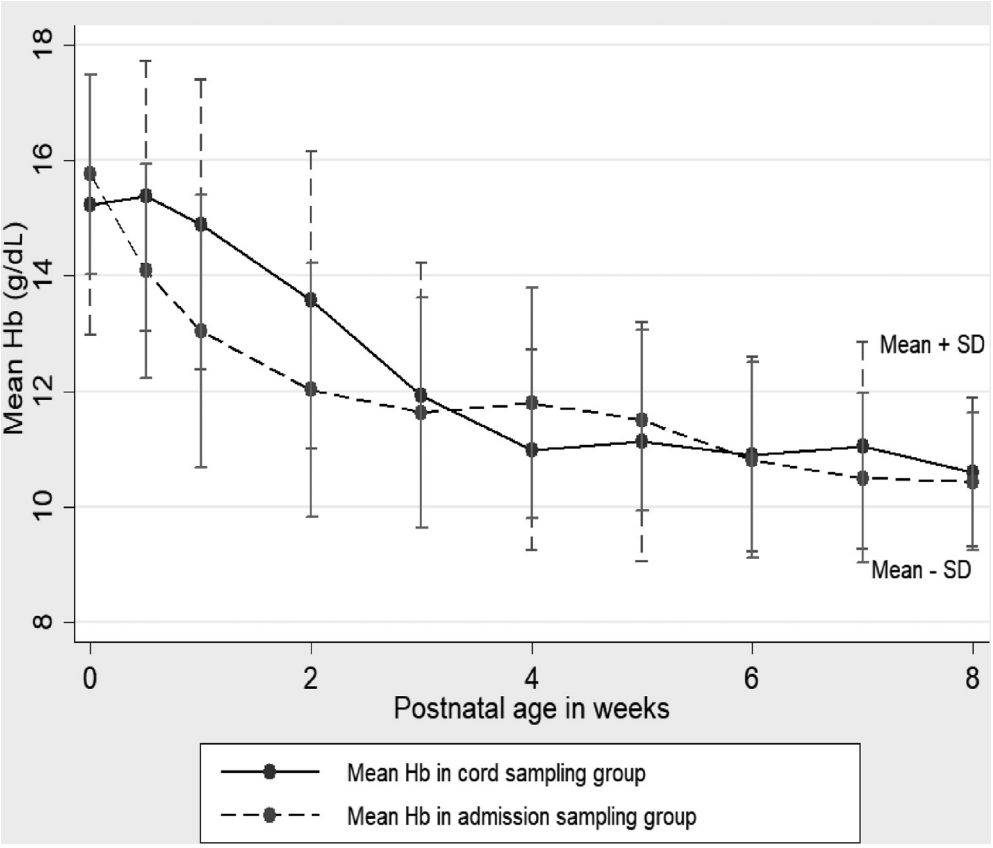

Figure 3. Comparison of mean hemoglobin (*Hb*) levels in both groups.