HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2018 November 08.

Published in final edited form as:

J Perinatol. 2018 August ; 38(8): 1022–1029. doi:10.1038/s41372-018-0120-0.

Anemia of Prematurity and Cerebral Near-Infrared Spectroscopy: Should transfusion thresholds in preterm infants be revised?

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Abstract

Objective—To determine the impact of progressive anemia of prematurity on cerebral regional saturation (C-rSO_2) in preterm infants and identify the hemoglobin threshold below which a critical decrease (>2 SD below the mean) in C-rSO_2 occurs.

Study design—In a cohort of infants born ≤30 weeks EGA, weekly C-rSO_2 data were prospectively collected from the second week of life through 36 weeks post-menstrual age (PMA). Clinically-obtained hemoglobin values were noted at the time of recording. Recordings were excluded if they were of insufficient duration (<1 hour) or if the hemoglobin was not measured within 7 days. Statistical analysis was performed using a linear mixed effects-model and ROC analysis. ROC analysis was used to determine the threshold of anemia where C-rSO_2 critically decreased >2 SD below the mean normative value (<55%) in preterm infants.

Results—253 recordings from 68 infants (mean EGA 26.9±2.1 weeks, BW 1025±287g, 49% male) were included. 29/68 infants (43%) were transfused during hospitalization. Mixed-model statistical analysis adjusting for EGA, BW, and PMA revealed a significant association between decreasing hemoglobin and C-rSO_2 ($p<0.01$) in transfusion-naïve infants but not in transfused infants. In the transfusion naïve group, using ROC analysis demonstrated a threshold hemoglobin of 9.5g/dL (AUC 0.81, $p<0.01$) for critical cerebral desaturation in preterm infants.

Conclusions—In transfusion-naïve preterm infants, worsening anemia was associated with a progressive decrease in cerebral saturations. Analysis identified a threshold hemoglobin of 9.5g/dL below which C-rSO_2 dropped >2 SD below the mean.

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Conflict of Interest Statement:

None of the authors have competing financial interests in relation to this work.

Introduction

Anemia of prematurity is a pervasive problem in the NICU, but its management remains an ongoing source of controversy.[1, 2, 3, 4] Resulting from low circulating erythropoietin, the lack of third trimester iron stores, decreased red blood cell lifespan, and phlebotomy losses, anemia of prematurity represents the intersection of transitional physiology and the sequelae of prematurity, with an even greater impact for critically-ill infants.[2, 5, 6] As a result of these factors, an estimated 85% of very low birth weight infants will receive a packed red blood cell (PRBC) transfusion during their hospitalization for treatment of their anemia.[7] Significant variation exists in transfusion practices and trials, such as the PINT trial, which have attempted to better define transfusion thresholds have yielded inconclusive results.[1, 3, 6, 8, 9, 10, 11, 12, 13] Existing data suggest no difference in short-term outcomes between liberal and restrictive transfusion practices and data on long-term outcomes are limited and conflicting.[1, 2, 3, 14, 15, 16] Post-hoc analysis of PINT study outcomes data demonstrate significantly better long-term cognitive outcomes in the liberal group and meta-analyses of neurologic outcomes favor liberal transfusion protocols, making it difficult to assume restrictive protocols are equivalent.[1, 3, 14]

As a result, clinicians currently lack evidence to guide them in their decision to transfuse a particular patient.[2, 3, 4, 16] Until further randomized control trial data become available, objective assessments of the impact of anemia on an individual infant's physiology are needed. Currently available clinical trials that evaluate low versus high thresholds for transfusing premature infants have largely ignored physiologic compensatory responses to progressive anemia. These responses are likely patient specific. Hence, establishing thresholds for PRBC transfusion needs to account for these patient specific compensatory responses and rely on measurement of end-organ tissue saturations. While data on the adaptation of preterm infants to anemia are limited, they have demonstrated higher cardiac output, higher oxygen extraction, and lower cerebral saturations in the setting of anemia, which improve with transfusion.[17, 18, 19, 20, 21]

Existing data also raise concerns about the impact of anemia on cerebral oxygen delivery and, therefore, on neurodevelopment.[1, 3, 14, 22] Current data estimate the incidence of neurodevelopmental impairment in extremely preterm infants at 25–50%.[23, 24, 25, 26] The underlying mechanisms for this injury are multifactorial and incompletely understood, but known causative factors include chronic hypoxia, hypoxia-ischemia, inflammation, and oxidative injury.[23, 27, 28, 29, 30] Abnormal neurodevelopment and white matter injury/loss are the most common pathologic and neuroimaging findings.[23, 27, 29] Animal models of chronic hypoxia have shown white matter injury patterns similar to those of preterm infants.[28, 30, 31] Anemia and the resultant decrease in oxygen carrying capacity presumably increase the burden of cerebral hypoxia in preterm infants, but currently data on the impact of progressive anemia on cerebral oxygenation are lacking.

Currently, the standard of care in preterm infants includes continuous measurement of peripheral arterial oxygenation by pulse oximetry, but does not include monitoring of regional tissue saturations. Pulse oximetry provides data on oxygen supply to the tissues, but not on tissue oxygen demand and utilization. Near-Infrared Spectroscopy (NIRS), a non-

invasive measure of mixed (predominantly venous) tissue saturation, provides a tool to assess patient-specific cerebral oxygenation at the bedside and identify anemic infants whose compensatory physiologic mechanisms have been overwhelmed resulting in a drop in cerebral oxygenation below the normative range.[19, 32, 33, 34, 35] Existing data from the first two weeks of life in premature infants suggest that the normative range of cerebral regional saturations (C-rSO_2) is 70 ± 15%.[21, 36]

In this study, we sought to examine the longitudinal impact of anemia of prematurity on cerebral regional oxygen saturation (C-rSO_2) in preterm infants and identify the threshold of hemoglobin below which a critical (defined as >2SD below mean for premature infants) decrease in C-rSO_2 occurs. Using NIRS, we prospectively evaluated the impact of increasing anemia on C-rSO_2 in a cohort of preterm infants less than 30 completed weeks estimated gestational age (EGA) through 36 weeks post-menstrual age (PMA).

Methods

Patient selection

In this prospective observational study, preterm infants born at or before 30 weeks completed gestation were recruited in the first 14 days of life from the St. Louis Children's Hospital NICU, a level IV unit serving an urban, suburban, and rural population. Infants were excluded if they had known congenital or chromosomal anomalies or they were clinically unstable and not expected to survive the first week of life. Informed written consent was obtained from parents for all participants. The study protocol and procedures were reviewed and approved by the Institutional Review Board of the Human Subjects Research Protection Office at Washington University.

Sample characteristics

Comprehensive sample characteristics were collected for all infants in our cohort. Antenatal characteristics included mode of delivery, antenatal corticosteroid exposure, and the five-minute Apgar score. Patient characteristics included EGA in completed weeks, birth weight, small for gestational age (SGA) status (defined as birth weight <10th centile), gender, and race/ethnicity. Clinical factors included Clinical Risk Index for Babies II (CRIB-II) score (using the algorithm developed by Parry et al.[37]), intraventricular hemorrhage (IVH [based on cranial ultrasound, graded using the Papile scoring system[38]]), respiratory support type and duration, medication administration, patent ductus arteriosus (PDA [based on echocardiographic diagnosis]), hemoglobin measurements, transfusions, and mortality. All hemoglobin values were obtained at clinical provider discretion.

Institutional practices and guidelines

Cerebral NIRS is not part of routine clinical monitoring of preterm infants at our institution. Institutional transfusion guidelines for premature infants recommend PRBC transfusion for hemoglobin ≤10 g/dL in critically-ill infants (defined as being intubated and ventilator dependent) and for hemoglobin ≤8 g/dL in stable, non-intubated infants. To reduce donor exposure, transfusions occur, whenever possible, from single-donor split units, administered in 15 mL/kg aliquots. All transfusions occur at clinician discretion.

Data collection

C-rSO_2 data were collected using NIRS via the INVOS 5100C oximeter with the OxyAlert Infant/Neonatal Sensor (Covidien, Mansfield, MA). The device utilizes a two-wavelength (730 and 810 nm) LED-based emitter and two optical detectors located 30 and 40 mm from the emitter, sampled at a rate of 0.2 Hz. The sensor was placed on the left frontoparietal scalp. Weekly cerebral NIRS recordings were conducted from the second week of life through 36 weeks PMA.

Recording analysis

Prior to analysis, all recordings were visually evaluated for quality and were eliminated if they were corrupted, of insufficient duration (<1 hour), or if a hemoglobin measurement was not obtained within 1 week of the recording. The 1-hour threshold for sufficiency of data duration was empirically determined by examining the duration of C-rSO_2 data required to obtain a stabilized mean within 10% of the value for a recording 8 hours in length (Figure 1). A mean C-rSO_2 value was computed for each recording.

Statistical Approach

Statistical analysis was performed using the software program IBM SPSS (IBM Corporation, Armonk, NY). Clinical characteristics of the transfused and non-transfused infants were compared in univariate analysis by the Mann–Whitney U-test for continuous variables and the Fisher's Exact test (two-sided) for categorical variables. To determine the effects of hemoglobin and other clinical variables on the C-rSO_2, we used the linear mixed-effects model procedure in SPSS.[39] The autoregressive covariance matrix (with heterogeneous variances) was used as the dependent variables were anticipated to diverge with time. Best-fitting models were identified for lowest values of the −2 log likelihood, Akaike's information criterion, and Schwarz's Bayesian criterion.[40] Due to the limited number of subjects in the study cohort and concern about model overfitting, multivariable analyses were limited to biologically plausible associations, to main effects for baseline measures, and time-dependent covariates for longitudinal measures. To ensure stability/reliability of estimates, 95% confidence intervals (CI) were re-estimated by bootstrapping (n=1000). To determine the hemoglobin threshold where the C-rSO_2 dropped >2SD below the normative mean for preterm infants (<55%), we computed receiver-operating characteristics (ROC) of hemoglobin values by plotting sensitivity *vs.* 1 – specificity.[41] To identify the hemoglobin value that best correlated with C-rSO_2 <55%, we selected the point with the highest sum of sensitivity and specificity (Youden's *J* statistic).[42] All statistical tests were two-tailed and considered significant at $p<0.05$.

Results

Demographic, perinatal, and delivery characteristics

This study included 68 infants with a mean±SD EGA of 26.9±2.1 weeks and mean±SD birth weight of 1025±287 grams. 29/68 (43%) of infants received at least one PRBC transfusion during hospitalization. The remaining 39 infants never received a transfusion. In general, the transfused infants were less mature (25.3 vs. 28.1 weeks, p<0.01), smaller (822 vs. 1175

grams, p<0.01), and sicker, with higher median CRIB-II scores (12 vs. 8, p<0.01), more inotrope therapy (28% vs. 0%, p<0.01), and higher mortality (14% vs. 0%, p=0.03) than their non-transfused counterparts. Full sample characteristics for both the transfused and non-transfused groups are listed in Tables 1 and 2.

Clinical and transfusion characteristics

During monitoring, 34% and 68% of all infants had a measured hemoglobin ≤8 and 10 g/dL respectively. The transfused group had a significantly higher proportion of patients with both hemoglobin ≤8 g/dL (52% vs. 21%, p=0.01) during monitoring. Of the 29 infants in the cohort who ever received transfusions, 26 (90%) received a transfusion after 7 days of life.

Data quality

A total of 312 C-rSO_2 recordings were obtained from the 68 infants included in the study. 253 recordings (81%) were included in the final analysis. The remaining 59 recordings were excluded due to missing/corrupted data (n=10), insufficient recording length (n=3), or absence of a hemoglobin measurement within 7 days (n=46). For the included recordings, the mean time differential between hemoglobin measurement and C-rSO_2 recording was 2.0±1.7 days. The median length of usable data in the included recordings was 3.6 hours (range 1.3–8.0 hours).

Mixed-effects model and ROC analysis

Linear modeling of the two groups revealed a weak statistically-significant correlation between hemoglobin and C-rSO_2 in the transfused group (r^2=0.04, p=0.02). There was a moderate statistically-significant correlation in the non-transfused group (r^2=0.24, p<0.01). Scatter plots of the hemoglobin and C-rSO_2 for both groups are illustrated in Figure 2.

Mixed-model statistical analysis adjusting for EGA, BW and PMA was used to examine the relationship between hemoglobin and C-rSO_2 in all infants. This analysis revealed a significant association between decreasing hemoglobin levels and C-rSO_2 (p<0.01) in the non-transfused group, but not in the transfused group. ROC analysis for all infants (transfused and non-transfused) demonstrated marginal discrimination (AUC 0.70, p<0.01), and a threshold hemoglobin of 9.2g/dL for critical cerebral desaturation (C-rSO_2< 55%).[36, 43] In the non-transfused group, ROC analysis demonstrated good discrimination (AUC 0.81, p<0.01), with a threshold hemoglobin of 9.5g/dL (Figure 3). In the transfused group, ROC analysis was not significant (AUC 0.57, p=0.17, Figure 3). The two groups were significantly different (p<0.001). The selected hemoglobin threshold represents the optimal combination of sensitivity and specificity (Youden's J statistic). The Youden's J statistic, sensitivity, and specificity used to select the hemoglobin threshold for the non-transfused infants are illustrated in Figure 4.

Discussion

These results demonstrate an association between an increasing degree of anemia and decreasing cerebral saturations in transfusion-naïve infants. This finding is consistent with prior investigation into physiologic adaptations to anemia in preterm infants, particularly that

anemic infants have lower cerebral saturations and higher oxygen extraction than non-anemic infants.[19, 35] Such a relationship was not seen in transfused infants, which is consistent with prior cross-sectional studies. A 2010 cross-sectional study by Bailey et al.[19] found no relationship between hemoglobin and C-rSO_2 in preterm infants with symptomatic anemia pre-transfusion, while a 2011 study from McNeill et al.[44] found a modest correlation between hemoglobin and C-rSO_2 in a small cohort of transfusion-naïve preterm infants in the first 21 days of life. One potential explanation for this difference is the cross-sectional nature of these studies whereas this study is a longitudinal one. Another variable is the introduction of adult hemoglobin following a transfusion, which has a different oxygen affinity than fetal hemoglobin, and may alter oxygen delivery in transfused infants.

Additionally, we found that the threshold for critical cerebral desaturation in non-transfused infants is approximately 9.5g/dL, implying a loss of physiologic compensation to anemia at a higher hemoglobin than previously thought. This threshold is significantly higher than that set by the PINT trial in both the low (≤8.5g/dL with respiratory support and ≤ 7.5g/dL without) and high (≤ 10g/dL with respiratory support and ≤ 8.5g/dL without) threshold groups after the first 2 weeks of life.[8] This raises the possibility that, outside of the post-hoc analysis, the PINT study's results were equivocal because the threshold for infants in both transfusion groups was set below the point of physiologic compromise.[8, 14] Infants in both groups may have experienced prolonged compromise of cerebral oxygen saturation (not measured as part of the trial) without reaching protocol transfusion thresholds, thus confounding the results.

When the entire cohort is considered, the threshold for critical cerebral desaturation appears to be 9.2g/dL. This is consistent with a prior cross-sectional study of 33 preterm infants undergoing transfusion which found a pre-transfusion hemoglobin of 9.7g/dL to be the threshold for cerebral desaturation and elevated FTOE in those infants.[45] However, since tissue oxygen delivery is dependent on cardiac output along with the oxygen carrying capacity of blood, the exact hemoglobin threshold is likely different for each individual infant. Routine longitudinal monitoring of cerebral oxygenation provides the opportunity to assess whether a particular degree of anemia has compromised cerebral oxygenation, aiding clinicians in deciding if a transfusion is needed in a particular patient.[32, 33, 35, 46] Regular surveillance, prior to reaching this threshold, offers a patient-specific bedside tool to determine when compensatory mechanisms for anemia have been overwhelmed, potentially putting the infant at risk of hypoxia-related white matter injury and adverse neurologic outcomes such as cerebral palsy. NIRS may provide a tool for determining individualized transfusion thresholds in a patient population where conclusive randomized control trial data are currently lacking and where evidence exists that severe anemia may be harmful to the developing brain.

This study has a few important limitations. First, the data collection for this cohort did not include pulse oximetry data. As a result, we were unable to exclude periods where the SpO_2 was less than 85% when C-rSO_2 values are considered less reliable. From review of monitoring data in other studies conducted by our group, and the NICU guidelines for target saturations in this population (90–95%), we know that preterm infants in our NICU spend the overwhelming majority of their time with SpO_2 greater than 90%, but we do not have

time-linked data in the present study.[47] Future study should include simultaneous capture of pulse oximetry data. Second, as our study was observational, our data relied on clinically-obtained hemoglobin measurements, which led to recordings without a recent hemoglobin being excluded from the analysis. While this deliberately conservative approach meant a 15% exclusion of recording data, it was aimed at ensuring accuracy of the analysis and avoiding spurious results from outdated hemoglobin values. This laboratory methodology is shared with the PINT study where hemoglobin measurement also occurred clinician discretion.[8] Finally, we had intentionally strict inclusion criteria for NIRS recordings to ensure that only good quality data representative of actual patient C-rSO_2 values were included. The 1-hour recording length criterion was based on empiric investigation, demonstrating that the mean value of C-rSO_2 derived from a 60-minute recording, closely approximated (no more than 10% deviation) the mean C-rSO_2 of a 6 to 8-hour recording. In this manner, we avoided inaccurate values from short, discontinuous recordings which only represented 1% of the overall recorded data.

Future directions for this research will include use of pulse oximetry to determine cerebral fractional tissue oxygen extraction (cFTOE). Utilizing, SpO_2 and C-rSO_2, calculation of cFTOE will allow for assessment of the balance between oxygen delivery and consumption in preterm infants. Increased cFTOE is a known adaptation to anemia that reverses with transfusion.[20, 21] Elevated cFTOE (≥0.4) has been associated with an increased risk of brain injury in infants ≤30 weeks, like those in our cohort.[48]

In conclusion, cerebral oximetry using NIRS provides a tool to assess for compromised cerebral oxygenation from anemia in transfusion naïve preterm infants. An increasing degree of anemia was associated with a progressive decrease in C-rSO_2, with a stronger correlation in transfusion-naïve infants. For infants who had never been transfused, the hemoglobin threshold for critical cerebral desaturation (C-rSO_2 <55%) was 9.5g/dL. Cerebral NIRS surveillance in these infants prior to reaching this threshold could aid in determining whether a transfusion is required.

Acknowledgments

Funding Sources:

This work was supported by the following grants:

1. Washington University Institute of Clinical and Translational Sciences KL2 Training Program (NIH/NCATS KL2 TR000450)
2. The Gerber Foundation
3. The Barnes-Jewish Hospital Foundation and the Washington University Institute of Clinical and Translational Sciences Clinical and Translational Funding Program (NIH/NCATS UL1 TR000448)
4. NIH award R01HL124078

The authors would like to thank our study coordinator, Anthony Barton, and our research assistant, Laura Atwood, for their tireless efforts. We also thank all the patients and families who participated in this study.

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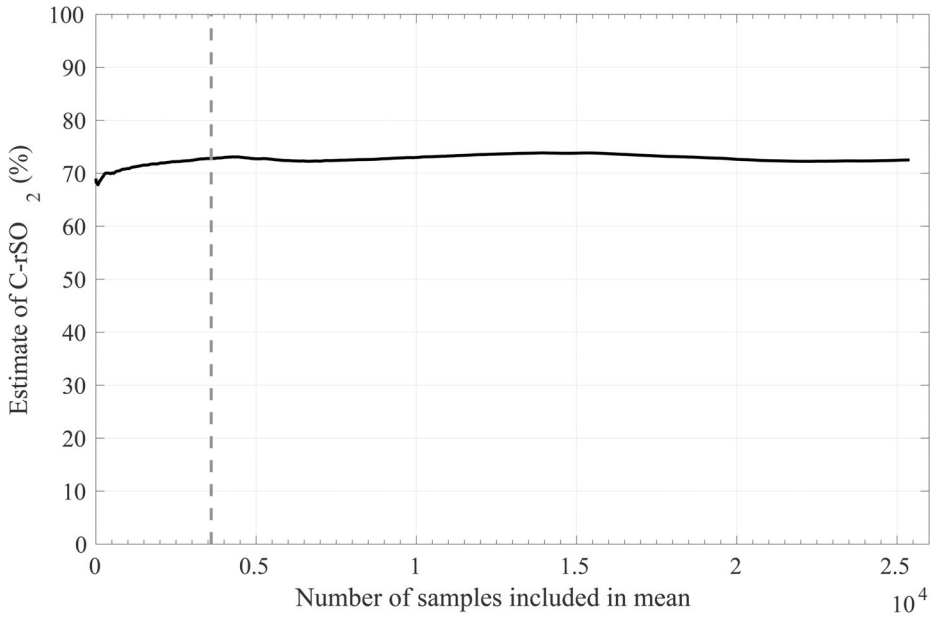


Figure 1.

A graphical illustration of the rolling average computation used to empirically derive the 1 hour (3,600 sample) minimum for recording length. Stabilization of the mean C-rSO_2 value of the above 7 hour (25,000 sample) recording occurs within the first hour (indicated by the dashed line). This was a consistent finding, demonstrating that 1 hour of data is sufficient to compute a mean C-rSO_2 value that is reflective of that of a 6–8 hour recording.

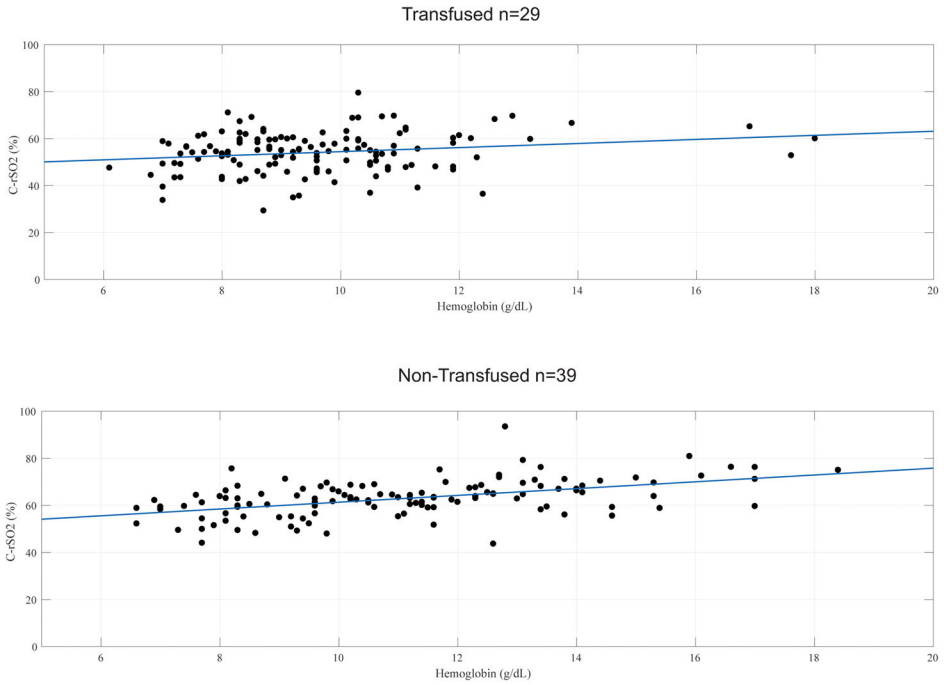


Figure 2.

Scatter plots illustrating the correlation between hemoglobin and C-rSO_2 in transfused (left) and non-transfused infants. Both groups exhibit statistically-significant positive correlations indicating that C-rSO_2 decreases with worsening anemia. The correlation is weak in the transfused group (r^2=0.04, p=0.02) and moderate in the non-transfused group (r^2=0.24, p<0.01).

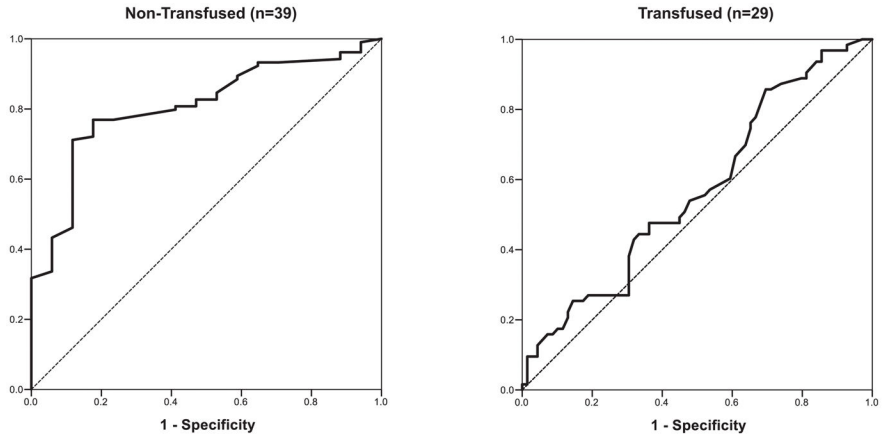
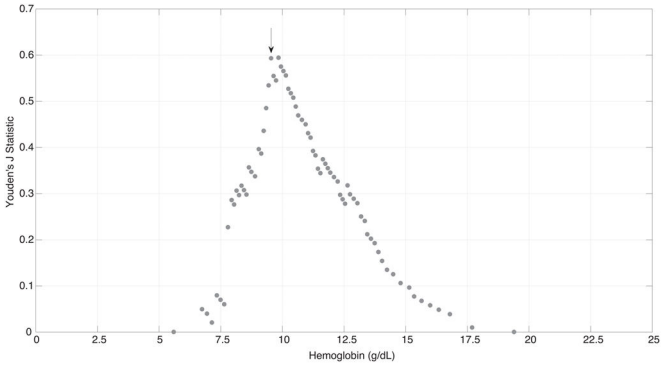


Figure 3.

ROC curves for all infants (left), transfused infants (middle), and non-transfused infants (right). ROC analysis was significant for all infants and the non-transfused group, but not for the transfused group (AUC 0.57, p=0.17). For all infants, there was marginal discrimination (AUC 0.70, p<0.01). For the non-transfused group, there was good discrimination (AUC 0.81, p<0.01).



Hemoglobin (g/dL)	Sensitivity	1-Specificity	Specificity	Youden's J
8.550	0.827	0.529	0.471	0.298
8.750	0.817	0.471	0.529	0.347
9.050	0.808	0.412	0.588	0.396
9.250	0.788	0.353	0.647	0.436
9.550	**0.769**	**0.176**	**0.824**	**0.593**
9.750	0.721	0.176	0.824	0.545
10.050	0.683	0.118	0.882	0.565
10.250	0.644	0.118	0.882	0.527
10.550	0.606	0.118	0.882	0.488

Figure 4.

The graph on the left displays the Youden's J statistic for each hemoglobin level in the non-transfused infants. The arrow indicates the point associated with the hemoglobin threshold of 9.5g/dL. The table on the right displays the sensitivity, specificity, and Youden's J statistic for each hemoglobin value with the chosen threshold, which maximizes sensitivity and Youden's J, highlighted in gray.

Table 1

Demographic and perinatal characteristics of transfused and non-transfused infants.

	Transfused (n=29)	Non-Transfused (n=39)	P value
EGA (weeks), mean (SD)	25.3 (1.6)	28.1 (1.6)	<0.01 *
BW (g), mean (SD)	822 (208)	1175 (240)	<0.01 *
Male sex, n (%)	16 (55%)	17 (44%)	0.46
Race/ethnicity, n (%)			
Caucasian	15 (52%)	16 (41%)	0.61
African-American	14 (48%)	22 (56%)	
Hispanic	0 (0%)	1 (3%)	
Antenatal steroids, n (%)			
Any	25 (86%)	30 (77%)	0.37
Complete	21 (72%)	23 (59%)	0.31
Cesarean delivery, n (%)	23 (79%)	32 (82%)	1.00
5-min Apgar, median (range)	5 (0–8)	7 (1–9)	<0.01 *
CRIB-II score, median (range)	12 (3–15)	8 (7–18)	<0.01 *
SGA[a], n (%)	4 (14%)	4 (10%)	0.72

Footnote:

* denotes statistical significance ($p<0.05$).

[a] SGA, small for gestational age, defined as BW <10th percentile.

Table 2

Clinical characteristics of transfused and non-transfused infants.

	Transfused (n=29)	Non-Transfused (n=39)	P value
Transfusion >7 days of life, n (%)	26 (90%)	-	-
Anemia during monitoring, n (%)			
Hemoglobin ≤ 10 g/dL	27 (93%)	19 (49%)	<0.01*
Hemoglobin ≤ 8 g/dL	15 (52%)	8 (21%)	0.01*
IVH, n (%)			
Any IVH	9 (31%)	9 (23%)	0.58
Grade III/IV IVH	2 (7%)	0 (0%)	0.18
Inotropic medication, n (%)			
During hospitalization	8 (28%)	0 (0%)	<0.01*
< 7 days of life	5 (17%)	0 (0%)	0.01*
BPD[a], n (%)	21 (81%)	10 (26%)	<0.01*
Home oxygen, n (%)	7 (28%)	4 (10%)	0.09
PDA treatment, n (%)			
No treatment	21 (41%)	7 (18%)	0.06
Medical treatment only	5 (17%)	6 (15%)	1.0
Surgical treatment only	1 (3%)	0 (0%)	0.43
Medical & surgical treatment	3 (10%)	0 (0%)	0.07
Necrotizing enterocolitis, n (%)	7 (24%)	0 (0%)	<0.01*
Discharge Z-score, mean (SD)	−0.76 (1.3)	−0.67 (1.1)	0.67
Mortality, n (%)	4 (14%)	0 (0%)	0.03

Footnote:

* denotes statistical significance ($p<0.05$).

[a] BPD, bronchopulmonary dysplasia, defined as persistent oxygen requirement at 36 weeks PMA.