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Associations of donor, component, and recipient factors on hemoglobin increments following red blood cell transfusion in very low birth weight infants

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Abstract

BACKGROUND: Anemia in very low birth weight (VLBW) infants is common and frequently managed with red blood cell (RBC) transfusions. We utilized a linked vein-to-vein database to assess the role of blood donor and component factors on measures of RBC transfusion effectiveness in VLBW infants.

STUDY DESIGN AND METHODS: We linked blood donor and component manufacturing data with VLBW infants transfused RBCs between 1/1/2013 and 12/31/2016 in the Recipient Epidemiology Donor Evaluation Study-III (REDS III) database. Using multivariable regression, hemoglobin increments and subsequent transfusion events following single-unit RBC transfusion episodes were examined with consideration of donor, component, and recipient factors.

RESULTS: Data on VLBW infants (n=254) who received one or more single-unit RBC transfusions (n=567 units) were linked to donor demographic and component manufacturing

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characteristics for analysis. Reduced post-transfusion hemoglobin increments were associated with RBC units donated by female donors (−0.24 g/dL [95% confidence interval (CI) −0.57, −0.02]; p=0.04) and donors < 25 years-old (−0.57 g/dL [95% CI −1.02, −0.11]; p=0.02). For RBC units donated by male donors, reduced donor hemoglobin levels were associated with an increased need for subsequent recipient RBC transfusion (odds ratio 3.0 [95% CI 1.3, 6.7]; p<0.01). In contrast, component characteristics, storage duration, and time from irradiation to transfusion were not associated with post-transfusion hemoglobin increments.

CONCLUSION: Donor sex, age, and hemoglobin levels were associated with measures of RBC transfusion effectiveness in VLBW infants. Mechanistic studies are needed to better understand the role of these potential donor factors on other clinical outcomes in VLBW infants.

BACKGROUND

Newborns experience a physiologic anemia following birth; hemoglobin level normally decreases in the first months of life and reaches its nadir, approximately 10 g/dL, at 6-12 weeks of age.[1,2] Causes of physiologic anemia are multifactorial, including low production of endogenous erythropoietin, a shorter red blood cell (RBC) lifespan of 40-60 days relative to 120 days in adults, and dilution of hemoglobin in the setting of rapid postnatal growth and increased circulating volume.[2] Physiologic anemia is usually well tolerated by term newborns; however, in preterm infants, the hemoglobin concentration drop is more severe and occurs earlier. Nadir hemoglobin levels may be as low as 7 g/dL at 4-8 weeks of age for newborns with birth weights <1200 g and 9 g/dL at 8-10 weeks of life for those with birth weights of 1200-2500 g.[2] In addition, premature infants are exposed to iatrogenic causes of anemia through frequent phlebotomy.[3]

Anemia in very low birth weight (VLBW) infants (≤1500 g) is often managed with RBC transfusions, and VLBW infants are one of the most transfused populations. Approximately half of VLBW infants receive RBC transfusion support following birth.[4,5] Therefore, an improved understanding of factors influencing the efficacy of RBC transfusion in this population is warranted.

Substantial variability is recognized in the hemoglobin dose and quality among RBC units. Blood donor biologic, genetic, and behavioral heterogeneity interacts with various manufacturing and storage conditions to influence both the red cell mass and storage quality of RBC units.[6–10] An improved understanding of the contribution of these variables to blood product composition may help improve RBC transfusion efficacy in VLBW infants and reduce their overall transfusion burden. In this retrospective study, we utilized a linked vein-to-vein database to examine associations of donor, component manufacturing and processing, and recipient factors on measures of RBC transfusion effectiveness in VLBW infants.

METHODS

We conducted a retrospective cohort study using electronic health records from the NHLBI REDS-III program utilizing public use data through BioLINCC. The database included blood donor, component, and recipient data collected at 12 academic and community

hospitals from four regions in the United States (Connecticut, Pennsylvania, Wisconsin, and California) for the 4-year period from January 1, 2013 to December 31, 2016. Only 7 of the 12 hospitals in the REDS-III program provided care to newborn infants and were included in this study. These 7 hospitals included both tertiary and quaternary centers, some of which performed cardiac and noncardiac surgery.[4] Data regarding blood donor demographics (e.g., age, sex, ABO/Rh), collection date and method (e.g., whole blood or apheresis), and component manufacturing characteristics (e.g., timing of leukoreduction, additive solution, irradiation status) were extracted for each RBC unit collected.

We included all VLBW infants (defined as a birth weight ≤1500 g) who received at least one RBC transfusion between January 1, 2013 and December 30, 2016. Recipient details included gestational age at birth, sex, and birth weight in grams, along with issue date of the transfused RBCs. Information on concurrent transfusion of other blood components (e.g., platelets, plasma) in the 12 hours prior to and following RBC transfusion was included. We collected hemoglobin levels measured by the clinical laboratory prior to and following each RBC transfusion event.

All single RBC transfusion episodes were included in this analysis. Only RBC aliquot volumes issued by the transfusion service were available, and not the actual volume administered. A RBC transfusion episode was defined as any single RBC transfusion linked to a donor with both informative pre- and post-transfusion hemoglobin levels and without additional RBC units transfused in the intervening period between lab draws. For pre-transfusion hemoglobin, the value used was the most proximal hemoglobin measurements, within the 24 hours prior to RBC transfusion. For post-transfusion hemoglobin, the laboratory measure closest to the end of transfusion but within 24-hours post-transfusion was utilized based on prior studies.[6,7]

Statistical Analysis

We linked donor, component, and transfusion recipient characteristics using product identification numbers for donations. Donor, component, and recipient variables (see Table 1) were included in multivariable linear regression models to examine associations with hemoglobin increments following RBC transfusion as the primary outcome. For the secondary outcome, multivariable logistic regression models were fit to evaluate the odds of additional RBC transfusion events occurring within 48 hours of the index event, adjusting for donor, component, and recipient characteristics (see Table 1).

Data are presented as counts and percentages, means with standard deviations (SD) or medians with interquartile ranges (IQRs). Accordingly, X^2 tests for equal proportion, t tests, or Wilcoxon rank sum tests were used to test differences. Multivariable linear regression results were reported as coefficients with 95% confidence intervals (CI) representing the mean hemoglobin increment following RBC transfusion for that variable. Accounting for donor, component, and recipient factors, multivariable logistic regression assessed associations between the covariates and the likelihood of subsequent RBC transfusion occurring within 48 hours of the index transfusion event. Two-sided p-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using Stata Version 14.1, StataCorp, College Station, TX.

RESULTS

We identified 254 VLBW infants who received 567 single-unit RBC transfusions for which relevant donor, component, and recipient data were available (Table 1). The median birth weight was 860 g (IQR 750-1110), gestational age was 25 weeks (IQR 24-26 weeks), and 39.8% of recipients were female. The pre-transfusion hemoglobin was 11.0 g/dl (SD: 1.8), the hemoglobin increment following transfusion was 1.9 g/dl (SD: 2.1), the number of days from birth to transfusion was 6 (IQR 2-15), and the number of RBC transfusions per infant was 2 (IQR 1-4). Concomitant plasma and platelet transfusions occurred in 17.2% and 24.3% of RBC transfusion episodes, respectively.

Median donor age was 52 years (IQR 36-59), 47.0% of RBC units were from female donors, and donor fingerstick hemoglobin level was 14.4 g/dL (SD: 1.1) with 28.7% (163/567) of donations in the lower range of acceptable hemoglobin levels (<13.5 g/dL). Nearly all RBC units were irradiated (98.8%), pre-storage leukoreduced (97.9%), and 100% were from group O donors. A minority of RBC units (11.3%) were apheresis-derived, the median aliquot volume issued from the blood bank was 26 mL/kg (IQR 20-38), the median RBC storage duration was 11 days (IQR 8-16), and the number of days from irradiation to transfusion was 3 days (IQR 0-8).

Table 2 shows regression estimates from the multivariate model for hemoglobin increments, estimating the mean hemoglobin increment after transfusion for each level change (for categorical variables) or unit increase (for continuous variables) of each predictor. Female donor sex (−0.24 g/dl [95% CI −0.02, −0.57]), donor age < 25 years-old (−0.57 g/dL [95% CI −1.02, −0.11]), male recipient sex (−0.36 g/dL [95% CI −0.35, −1.50]), increasing pre-transfusion hemoglobin levels (−0.70 g/dL [95% CI −0.79, −0.61]), and concomitant plasma transfusion (−0.64 g/dL [95% CI −1.06, −0.23]) were significantly associated with reduced post-transfusion hemoglobin increments in VLBW infants. When excluding concomitant platelet and plasma transfusions, coefficients for female donor sex (−0.28 g/dl [95% CI 0.04, −0.59]) and donor age < 25 years-old (−0.57 g/dL [95% CI −1.00, 0.14]) were not relevantly changed. Apheresis blood collection, aliquot volume issued, days from irradiation to transfusion, and storage duration were not associated with post-transfusion hemoglobin increments.

Additional RBC transfusion events occurred within 48 hours of the index transfusion in 72% (182/254) of VLBW infants. In univariate analysis, there were no differences in the need for subsequent transfusions in relation to donor age (p=0.59), apheresis collection (p=0.63), or donor sex (p=0.50). However, RBC units from male donors with hemoglobin levels <13.5 g/dL were associated with a higher incidence of a subsequent RBC transfusion (81% vs. 64%; p=0.04) within 48 hours of the index transfusion. As compared to those from other male donors, RBC units from male donors with hemoglobin levels <13.5 g/dL were associated with increased likelihood of a subsequent transfusion event within 48 hours (adjusted odds ratio 3.0 [95% CI 1.3, 6.7]; p<0.01).

DISCUSSION

Using a multivariable regression approach, we identified several donor and recipient factors associated with hemoglobin increments following RBC transfusion in VLBW infants. Reduced post-transfusion hemoglobin increments were associated with RBC units donated by female donors and younger donors (age < 25 years-old). For recipients of RBC units from male donors, reduced donor hemoglobin levels were associated with a need for subsequent RBC transfusion events. In contrast to prior studies, component characteristics and storage duration were not associated with post-transfusion hemoglobin increments; however, variability in these factors was limited.[6,7]

Premenopausal females are known to have higher rates of iron deficiency relative to other donor groups, which may contribute to qualitative RBC defects and corresponding reduced hemoglobin increment in recipients.[11,12] In contrast, RBCs donated from males have been shown to have higher rates of osmotic and oxidative hemolysis following prolonged cold storage.[13] In addition, blood donations collected from frequent donors with low ferritin may have increased susceptibility to hemolysis with prolonged storage.[14] These findings may not have direct clinical relevance for neonatal transfusion recipients who typically receive fresher RBC units. In our study, reduced donor hemoglobin levels in male donors were associated with the need for subsequent transfusion. Repeat transfusion exposes VLBW infants to potential metabolic, infectious, and immunologic complications. While speculative, reduced hemoglobin levels and the increased need for subsequent transfusion may be related to hemolysis of the red cells from these male donors.[12]

Biologic heterogeneity in blood donors may contribute to differences in the quality of blood components and transfusion outcomes in VLBW infants. While prior publications have been inconsistent, a recent study found RBC transfusions from female donors were associated with a lower risk of death or serious morbidity in VLBW infants.[15] While these findings are unlikely to be explained by reduced hemoglobin increments seen with female donors, other potential mechanisms, such as differences in blood viscosity related to donor sex, were proposed by the authors. Studies examining donor-specific genetic, hemolytic, and metabolomic data to evaluate potential mechanisms of the above findings are needed.

Not surprisingly, the majority of transfusion events in VLBW infants involved RBCs that were whole blood derived, irradiated, leukoreduced, and relatively fresh, which made analysis of these covariates limited. Also not surprisingly, the majority of RBC units used additive solutions lacking mannitol, likely due to concerns regarding mannitol toxicity in infants.[16] For recipients, male sex and pre-transfusion hemoglobin levels were associated with reduced hemoglobin increments following RBC transfusion. This finding is consistent with adult recipients and thought to be related to relative differences in circulating blood volumes.[6] In contrast to findings in adults, higher recipient weight was associated with increased hemoglobin increments in VLBW infants; this improved response to transfusion may reflect resolution of hemorrhage or bone marrow recovery occurring with infant growth or the frequency of blood sampling and relative magnitude of blood loss caused by laboratory testing in the smallest infants. Our study has several limitations. First, the bleeding status and specific clinical diagnoses of patients in the study is unknown, and

therefore the associations observed must be interpreted with caution and verified in future studies. VLBW infants receiving plasma transfusions had reduced hemoglobin increments following RBC transfusion, but these findings may be explained by underlying bleeding. However, our findings related to donor sex and age were unchanged when excluding RBC transfusion episodes that included concomitant plasma and platelet components. In addition, while aliquot volumes released from the transfusion service were available, the actual administered transfused volumes were not. Lastly, important details on differing neonatal transfusion practices at the seven REDS-III hospitals, such as those related to transfusion service aliquot practices, were not available and may influence the results observed.

In conclusion, donor sex and age were associated with hemoglobin increments following single-unit RBC transfusion to VLBW infants. Decreased hemoglobin levels in male blood donors were associated with the need for subsequent RBC transfusion events. Mechanistic studies are needed to better understand the role of the identified donor factors on other clinical outcomes in VLBW infants.

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Table 1:

Blood Donor, Component, and Transfusion Recipient characteristics

N (transfusion episodes)	**(n = 567)**
Blood Donor Characteristics	
Sex (% male)	302 (53.2%)
Age in years, median (IQR)	52 (36-59)
<25	86 (15.1%)
26-45	117 (20.5%)
46-69	263 (46.1%)
70+	105 (18.4%)
(+) Rh status (%)	232 (41%)
ABO status (%)	
O	567 (100%)
Donor smoking (%)	49 (8.7%)
Hemoglobin level in g/dL, mean (IQR)	14.4 (1.1)
Male ≥13.5 g/dL (%)	269 (47%)
Male <13.5 g/dL (%)	33 (6%)
Female ≥13.5 g/dL (%)	132 (23%)
Female <13.5 g/dL (%)	130 (23%)
Blood Component Characteristics	
Apheresis-derived (%)	64 (11.3%)
Irradiated (%)	560 (98.8%)
Days from irradiation to transfusion, median (IQR)	3 (0-8)
Pre-storage leukoreduction (%)	555 (97.9%)
RBC storage duration in days, median (IQR)	11 (8-16)
Storage solution (%)	
AS-1	90 (15.9%)
AS-3	366 (64.5%)
CPDA	111 (19.6%)
Issued aliquot volume in mL/kg, median (IQR)	26 (20-38)
Transfusion Recipient Characteristics	**N=254 infants**
Sex (% male)	153 (60.2)
Gestational age (in weeks)	
≤23	23 (9.3%)
24	48 (19.4%)
25	111 (44.8%)
26-27	38 (15.3%)
≥28	28 (11.3%)
Birth weight in grams (%)	

N (transfusion episodes)	**(n = 567)**
Blood Donor Characteristics	
≤750	64 (25.2)
751-1000	101 (39.8)
1,001-1,250	56 (22.1)
1,251-1,500	33 (13.0)
(+) Rh status (%)	160 (88.9%)
ABO status (%)	
A	27.8
B	15.0
AB	7.2
O	50.0
Pre-transfusion hemoglobin in g/dL, mean (SD)	11.0 (1.8)
Pre-transfusion hemoglobin in g/dL, median (IQR)	10.9 (9.9-11.9)
Post-transfusion hemoglobin in g/dL, mean (SD)	12.9 (1.8)
Hemoglobin increment in g/dL, mean (SD)	1.9 (2.1)
Number of transfusion episodes, median (IQR)	2 (1-4)
Concomitant platelet transfusion (%)	138 (24.3%)
Concomitant plasma transfusion (%)	92 (17.1%)

Table 2:

Regression estimates for hemoglobin increments after RBC transfusion for VLBW infants (n = 567)*

Characteristic	Hemoglobin increment in g/dL (95% CI)	p-value
Female donor	−0.24 (−0.57, −0.02)	0.04
Donor age (ref: 46-70 years)		
<25	−0.57 (−1.02, −0.11)	0.02
26-45	−0.19 (−0.55, 0.17)	0.31
70+	−0.32 (−0.78, 0.13)	0.17
Donor Rh positive status	−0.02 (−0.33, 0.28)	0.88
Donor hemoglobin	−0.01 (−0.03, 0.01)	0.29
Apheresis blood collection	0.45 (−.23, 1.13)	0.20
Leukoreduction	−0.60 (−1.49, 0.28)	0.18
RBC additive solution (ref: AS-1)		
AS-3	0.37 (−0.21, 0.95)	0.21
CPDA	−.13 (−0.80, 0.53)	0.69
Irradiation	−0.20 (−1.00, 1.40)	0.74
Days from irradiation to transfusion	−0.01 (−0.04, 0.02)	0.47
Storage duration in days	−0.01 (−.03, 0.01)	0.53
Aliquot volume in ml/kg	−0.00 (−0.00, 0.00)	0.43
Male recipient	−0.36 (0.35, 1.50)	<0.001
Recipient weight in kg	0.39 (0.17, 0.61)	<0.001
Recipient Rh positive status	0.15 (−0.55, 0.84)	0.68
Pre-transfusion hemoglobin level	−0.70 (−0.79, −0.61)	<.001
Concomitant plasma transfusion	−0.64 (−1.06, −0.23)	0.003
Concomitant platelet transfusion	−0.08 (−0.43, 0.28)	0.67

VLBW=very low birth weight; RBC=red blood cell; Hb=hemoglobin level (g/dL); Tx=transfusion

*Multivariable regression estimates estimating the mean hemoglobin increment after transfusion accounting for donor, component, and recipient characteristics presented in Table 1