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Red Blood Cell Transfusion Is Not Associated with Necrotizing Enterocolitis: A Review of Consecutive Transfusions in a Tertiary Neonatal Intensive Care Unit

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Abstract

Objective—To explore the association between red blood cell transfusion and necrotizing enterocolitis (NEC) in a neonatal intensive care unit with liberal transfusion practices.

Study design—A retrospective cohort study was conducted for all infants weighing <1500 g who received at least 1 packed red blood cell transfusion between January 2008 and June 2013 in a tertiary neonatal intensive care unit. The primary outcome was NEC, defined as Bell stage II or greater. The temporal association of NEC and transfusion was assessed using multivariate Poisson regression.

Results—The study sample included 414 very low birth weight infants who received 2889 consecutive red blood cell transfusions. Twenty-four infants (5.8%) developed NEC. Four cases of NEC occurred within 48 hours of a previous transfusion event. Using multivariate Poisson regression, we did not find evidence of a temporal association between NEC and transfusion ($P = .32$).

Conclusion—There was no association between NEC and red blood cell transfusion. Our results differ from pre vious studies and suggest that the association between NEC and transfusion may be contextual.

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The authors declare no conflicts of interest.

Necrotizing enterocolitis (NEC) is a major cause of morbidity and mortality among very low birth weight (VLBW) infants.[1-3] Several risk factors for NEC, including prematurity, use of formula, and aggressive feeding strategies, have been well established.[4-7] However, there is no consensus in the literature regarding the risk of developing NEC within 48 hours of packed red blood cell (pRBC) transfusion, known as transfusion-associated NEC (TA-NEC) or transfusion-related acute gut injury.[8-10]

Multiple retrospective cohort and case control studies have demonstrated an association between pRBC transfusion and subsequent development of NEC,[11-24] although 2 of these studies reported mixed results.[18,24] The risk of developing TA-NEC is reported to be 5-17 per 1000 transfusion events, accounting for 27%-38% of all NEC cases.[11,12,14,15,18] These observational studies have led to the growing acceptance of TA-NEC as a valid clinical entity.[9,10] Two studies have explicitly endorsed the practice of withholding enteral feeds during pRBC transfusion to avoid NEC,[16,25] and many institutions and practitioners have adopted this policy.[26] However, a recent meta-analysis of data from 3 randomized trials on transfusion thresholds for premature infants demonstrated no difference in the incidence of NEC with more liberal transfusion practices.[8,27-29]

The question of association between NEC and transfusion is important because neonates are among the most heavily transfused patient populations. Between 50% and 94% of VLBW infants receive at least 1 transfusion during their hospital stay, due to frequent laboratory testing and immature hematopoietic systems.[15,28,30,31] An accurate assessment of the risks associated with pRBC transfusion is essential for clinical decision making in the neonatal intensive care unit (NICU). In addition to the well-known risks of blood products, such as infection or graft-vs-host disease, clinicians need to consider the potential risk of developing NEC from transfusions. Previous studies on this topic were performed in NICUs with relatively restrictive transfusion practices, which may have influenced their assessment of the relationship between transfusion and NEC. Our primary aim is to evaluate the association between NEC and transfusion among VLBW infants in a tertiary NICU with liberal transfusion practices.

Methods

A retrospective cohort study was conducted for all VLBW infants <1500 g who received at least 1 pRBC transfusion between January 2008 and June 2013 in the Level IV NICU at Lucile Packard Children's Hospital at Stanford. This study was approved by the Stanford University Institutional Review Board.

Transfusion data were obtained by searching the Stanford University Blood Center database for all pRBC transfusions that were administered to patients in the NICU during the study period. These data were cross-tabulated with an electronic database to identify all transfusions that occurred in infants with birth weight <1500 g. This convenience sample was chosen to ensure that all included patients received a standardized feeding protocol, which was initiated in April 2007. Patients diagnosed with NEC at an outside hospital prior to transfer were excluded. There were no additional exclusion criteria. Transfusion events were noted for each patient until the time of transfer out of the NICU, hospital discharge, or

death. Demographic, maternal, and postnatal variables were collected, as well as the primary outcome measure of NEC.

Enteral Feeding Practices

The standardized feeding protocol in our NICU consists of 6 days of trophic feeds (20 mL/kg/day) followed by daily advancements of 20 mL/kg/day to reach a goal of 160 mL/kg/day for infants with birth weights of 1001-1500 g. For infants ≤1000 g, the protocol consists of trophic feeds for eight days (10 mL/kg/day for 4 days, followed by 20 mL/kg/day for 4 days), followed by daily advancements of 20 mL/kg/day to reach a goal of 160 mL/kg/day. Use of maternal breast milk or banked breast milk was highly encouraged for all VLBW infants.

Transfusion Practices

Transfusion decisions were made at the discretion of the attending neonatologist. Our unit does not have transfusion guidelines or hematocrit threshold policies. Each pRBC transfusion consisted of 10-20 mL/kg given over 2-4 hours. There is no unit policy on use of diuretics during transfusion. All transfusions were cytomegalovirus-negative, irradiated, type specific or type O, and Rh-compatible red blood cells in Adsol preservation solution (Fenwal Inc, Lake Zurich, Illinois). All pRBC units were less than 7 days of age from initial preservation to first use, but were kept until 42 days from initial preservation for repeat transfusions for the same patient. We do not have a policy of withholding feeds during transfusion, and it is not common practice in our unit, but practitioners may have pursued this strategy on an individual basis.

Definitions

NEC was defined as Bell stage II or greater.[32] All cases of NEC had radiographic and clinical evidence of NEC. Classification of NEC was performed by an attending neonatologist, who was blinded to the timing of transfusion events when reviewing patient charts. TA-NEC was defined as NEC that occurred within 48 hours after initiation of pRBC transfusion.

Statistical Analyses

Statistical analysis was performed using SAS version 4.1 (SAS Institute, Cary, North Carolina). Appropriate measures of central tendency were used to describe the data, including mean ± SD and median and IQR for continuous variables. Binary and categorical variables were described using frequencies and percentages. Patients with NEC and patients without NEC were compared using the Student t test, χ^2 test, Wilcoxon rank-sum test, and Fisher exact test as appropriate. Statistical significance was set at $P < .05$.

The rate of NEC per 1000 transfusion events was determined. We compared the number of transfusions given to patients who developed NEC to those who did not develop NEC, excluding transfusions that occurred after a diagnosis of NEC was made. This analysis is similar to that performed by 3 previous cohort studies on the same topic.[11,22,23] To assess the effect of anemia on TA-NEC, we compared pretransfusion hematocrit from TA-NEC cases to pretransfusion hematocrit of 50 control infants. This control group was a randomly

selected convenience sample among the set of transfused VLBW infants within the study period and had demographics similar to the overall cohort.

In a separate analysis, the association between NEC and pRBC transfusion was assessed using a multivariate Poisson regression with adjustment for potential confounding variables. For each patient, we created 48-hour epochs from birth or hospital admission through 32 weeks postmenstrual age (PMA), death, or hospital discharge. Given that the risk of NEC rapidly declines after 32 weeks PMA for VLBW infants,[33] epochs beyond 32 weeks PMA were excluded a priori, in an effort to avoid differential inclusion of events and non-events during epochs with a low baseline risk of NEC. Furthermore, none of the cases of TA-NEC in our dataset were excluded using these methods. We classified each epoch as having: (1) NEC or no NEC; and (2) transfusion or no transfusion. If diagnosis of NEC occurred before transfusion but within the same epoch as the transfusion, the transfusion in question was bumped to the subsequent epoch for coding purposes, which is similar to the method used in previous analyses.[17]

Using generalized estimating equations for longitudinal data with a Poisson distribution, we explored the association of NEC and pRBC transfusion in a model of consecutive 48-hour epochs. In addition to presence or absence of transfusion in each epoch, we included post-natal age in the analytic model as a potentially confounding binary variable in a predetermined range associated with the highest risk for NEC (6-14 days of life).[34] In a separate chi-squared analysis, we examined the expected vs observed rate of NEC in consecutive post-transfusion epochs.

Results

There were 414 VLBW infants who received 2889 consecutive pRBC transfusions. Twenty-four infants (5.8%) developed NEC. Four cases of NEC (17%) occurred within 48 hours of a prior pRBC transfusion, yielding a TA-NEC rate of 1.5 cases per 1000 transfusion events.

Infants who developed NEC had lower birth weights ($P = .03$). Other demographic and postnatal characteristics, including mortality, were no different between the two groups (Table I). The rates of malformations, genetic anomalies, and previous intestinal surgeries were also no different between the two groups ($P = .32$-$.99$). The majority of previous intestinal surgeries were related to small bowel atresia (40%) and spontaneous intestinal perforation (40%), with the remainder related to malrotation, omphalocele, and gastroesophageal reflux, among others.

The average PMA at diagnosis of NEC for all cases was 209 days (29 + 6/7 weeks) ± 20 days. The NEC group received more pRBC transfusions ($P < .001$), including 46% who received a pRBC transfusion in the 24 hours following the diagnosis of NEC. However, after excluding transfusions occurring after diagnosis of NEC, there was no difference in number of transfusions between the two groups (Table I).

For the regression analysis, we included a total of 5825 48-hour epochs for 383 VLBW infants, who received a total of 2242 pRBC transfusions over a period of 1754 epochs. Thirty-one infants were excluded from the regression analysis because their first hospital

day at our institution occurred beyond 32 weeks PMA. There were 4 cases of TA-NEC and 16 cases of non-TA-NEC included in the analysis. Four cases of non-TA-NEC occurred beyond 32 weeks PMA and were excluded as a result. Using multivariate Poisson regression, we did not find a temporal association between NEC and transfusion, aOR 0.57 (0.19-1.72), $P = .32$. We also found no association between the outcome of NEC and post-natal age, which was included in the analytic model ($P = .74$). Our sample size of 5825 epochs was sufficient to have a 99% probability of detecting a difference as large or larger than that reported in a prior analysis on this topic.[17] We found no difference in the expected vs observed rate of NEC by post-transfusion epoch (Table II).

There was no difference in age at diagnosis between TANEC and non-TA-NEC cases (23 ± 10 days vs 26 ± 19 days, $P = .66$). There was also no difference in pretransfusion hematocrit between the TA-NEC group and 50 randomly-selected control infants, 30 ± 4% vs 32 ± 4%, $P = .44$.

Characteristics of the four cases of TA-NEC are shown in Table III. One case of TA-NEC had a previous diagnosis of stage I NEC on day of life 9 and 2 cases of TA-NEC occurred within 3 days after patent ductus arteriosus ligation. Three of the 4 patients with TA-NEC were nil per os during the transfusion preceding diagnosis of NEC (Table III).

Discussion

We were unable to find an association between NEC and red blood cell transfusion. We found that the risk of TA-NEC was 1.5 cases per 1000 transfusion events, which is an order of magnitude smaller than the risk cited in previous reports.[11,12,15]

Our results differ from previous studies and suggest that the association between NEC and transfusion may be contextual, depending on clinical practice differences between centers. Our patients received more transfusions on average than other cohorts (Table IV). It is possible that our liberal transfusion practices were protective against TA-NEC, in that we avoid extremely low hematocrits that may predispose to reperfusion injury during transfusion. However, we found no difference in the pretransfusion hematocrit between TA-NEC cases and controls, suggesting that anemia likely did not play a significant role in development of TA-NEC in our dataset.

Alternatively, it is possible that subtle, prodromal signs of early NEC (eg, changes in heart rate[35]) may be treated with transfusion to correct an incidental finding of anemia in the laboratory evaluation of these prodromal signs. When NEC is subsequently diagnosed, it may be attributed to the transfusion, despite the incidental nature of the association. In the setting of more liberal transfusion practices, it is less likely that an infant with early NEC will be anemic and also less likely that transfusions will occur preferentially under these circumstances. The present study and a recent meta-analysis of pooled data (some unpublished) from 3 randomized trials are consistent with this hypothesis.[8,27-29]

Our method of compiling data from 2889 consecutive transfusions in VLBW infants over a 4.5-year period allowed us to avoid biases of selection inherent to case control study designs. Likewise, all infants included in our study were born after implementation of a

standardized feeding protocol,[7] which eliminated a potential confounding variable from our analysis.[4,7,36]

There are several limitations that should be considered. First, the generalizability of our results is uncertain, because our patient population was derived from a single, tertiary NICU. Second, we included only those patients who received at least 1 pRBC transfusion during their hospital stay. However, we do not believe that this affected our results or conclusions. Historically, approximately 80% of VLBW infants in our NICU receive at least one transfusion. Third, extensive statistical comparison of patients with TANEC to those patients with non-TA-NEC was not possible due to small numbers. Finally, our study is observational and retrospective, and may have the same biases inherent to previous cohort studies on this topic.

In conclusion, we were unable to find an association between NEC and red blood cell transfusion. Many neonatologists have already changed clinical practice in an attempt to avoid TA-NEC and are withholding enteral feeds before, during, and after blood transfusions —which may not be an entirely benign intervention. Further study of this relationship is needed prior to endorsing such changes in clinical practice.

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Glossary

NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
pRBC	Packed red blood cell
TA-NEC	Transfusion-associated necrotizing enterocolitis
VLBW	Very low birth weight

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Table I Demographic, maternal, and postnatal characteristics

Characteristics	NEC (n = 24)	No NEC (n = 390)	*P* value
Gestational age, wk, median (IQR)	27 (3)	27 (3)	.53
Birth weight, g, median (IQR)	790 (290)	900 (350)	.03
Female sex, n (%)	11 (46)	187 (48)	.82
Race, n (%)			
African-American	1 (4)	12 (3)	
Caucasian	2 (8)	128 (33)	
Latino	15 (63)	148 (38)	
Asian	6 (25)	86 (22)	
Other	0 (0)	16 (4)	.07
Antenatal steroids (completed course), n (%)	13 (54)	238 (61)	.50
Cesarean delivery, n (%)	16 (67)	285 (73)	.51
Apgar score at 1 min, median (IQR)	5 (5)	5 (5)	.82
Apgar score at 5 min, median (IQR)	7 (5)	7 (2)	.50
PDA, n (%)	14 (58)	207 (53)	.61
Intestinal malformation, n (%)	1 (4)	16 (4)	.94
Any malformation, n (%)	5 (21)	74 (19)	.82
Genetic anomaly, n (%)	1 (4)	16 (4)	.99
Previous intestinal surgery, n (%)	2 (8)	20 (5)	.32
Deceased, n (%)	2 (8)	39 (10)	.93
Total transfusions during hospitalization, mean ± SD	13 ± 8	7 ± 6	<.001
Total transfusions, excluding those after NEC diagnosis, mean ± SD	6 ± 7	7 ± 6	.45

PDA, patent ductus arteriosus.

Table II

Frequency of NEC by posttransfusion epoch*

	Posttransfusion epoch				
	0-2 d	3-4 d	5-6 d	7-8 d	>8d
Epochs with NEC	4	2	4	2	3
Epochs without NEC	1750	1012	704	505	1358
NEC rate per epoch, %	0.23	0.20	0.57	0.40	0.22

No difference in expected vs observed rate of NEC by posttransfusion epoch; $P = .58$.

*Excludes epochs with no previous transfusions.

Table III

Characteristics of TA-NEC cases

	Case 1	Case 2	Case 3	Case 4
Gestational age, wk	23.3	27.4	24.7	24.1
Birth weight, g	640	730	610	740
Sex	Male	Male	Female	Female
Race	Caucasian	Hispanic	Hispanic	Hispanic
Age at NEC, d	14	35	14	24
Time from transfusion to NEC, h	6	14	38	6
Transfusions before NEC diagnosis, n	9	7	7	5
Hematocrit before transfusion	35	29	28	27
Enteral feeding during transfusion?	No	Yes (165 mL/kg/d)	No	No
Intubated at time of transfusion?	Yes	No	Yes	No
Surgical NEC	Yes	No	No	No
Antenatal steroids (complete course)	No	Yes	Yes	Yes
Cesarean delivery	No	Yes	No	No
PDA	Yes	No	Yes	Yes
Deceased	Yes	No	No	No
Comments	-	Previous stage I NEC at age 9 d	Developed NEC at 3 d after PDA ligation	Developed NEC at 1 d after PDA ligation

Table IV

Comparison of cohort studies: differences in transfusion practices and rate of NEC

	Average number of transfusions per VLBW infant	Rate of NEC (cases per 100 infants)	Rate of TA-NEC (cases per 1000 transfusion events)
Present study	6.5	5.8	1.5
Paul et al[11]	2.8	5.3	5
Mally et al[12]	0.8	1.8	8
Blau et al[13]	Not available	14.1	Not available
Valieva et al[15]	3.8	13.3	17
Bak et al[22]	2.9	10	Not available
Carter et al[23]	5.7	11.8	Not available