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Feeding Practices and Other Risk Factors for Developing Transfusion-Associated Necrotizing Enterocolitis

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Abstract

Aims—Determine the incidence of and risk factors for necrotizing enterocolitis (NEC) and transfusion-associated NEC (TANEC) in very-low-birth-weight (VLBW) infants pre/post implementation of a peri-transfusion feeding protocol.

Study Design—A retrospective cohort study was conducted including all inborn VLBW infants admitted to the Duke intensive care nursery from 2002–10. We defined NEC using Bell's modified criteria IIA and higher and TANEC as NEC occurring within 48 hours of a packed red blood cell (pRBC) transfusion. We compared demographic and laboratory data for TANEC vs. other NEC infants and the incidence of TANEC pre/post implementation of our peri-transfusion feeding protocol. We also assessed the relationship between pre-transfusion hematocrit and pRBC unit age with TANEC.

Results—A total of 148/1380 (10.7%) infants developed NEC. Incidence of NEC decreased after initiating our peri-transfusion feeding protocol: 126/939 (12%) to 22/293 (7%), P=0.01. The proportion of TANEC did not change: 51/126 (41%) vs. 9/22 (41%), P>0.99. TANEC infants were smaller, more likely to develop surgical NEC, and had lower mean pre-transfusion hematocrits prior to their TANEC transfusions compared with all other transfusions before their NEC episode: 28% vs. 33%, P<0.001. Risk of TANEC was inversely related to pre-transfusion hematocrit: odds ratio 0.87 (0.79–0.95).

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Conflicts of Interest Dr. DeRienzo has received honoraria from hospitals to speak on quality and patient safety, and compensation from Doximity, Inc within the previous 12 months. Dr. Smith receives salary support for research from the National Institutes of Health and the U.S. Department of Health and Human Services (NICHD 1K23HD060040-01, DHHS-1R18AE000028-01, and HHSN267200700051C); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). The remaining authors declare that they have no conflicts of interest to disclose.

Conclusions—Pre-transfusion hematocrit is inversely related to risk of TANEC, which suggests that temporally maintaining a higher baseline hemoglobin in infants most at risk of NEC may be protective. The lack of difference in TANEC pre-/post-implementation of our peri-transfusion feeding protocol, despite an overall temporal decrease in NEC, suggests other unmeasured interventions may account for the observed decreased incidence of NEC.

Introduction

Necrotizing enterocolitis (NEC) is a severe intestinal disease affecting thousands of premature infants each year.[1] Mortality is >50% in infants with NEC who require surgery, while those who survive are at higher risk of lifelong neurodevelopmental impairment.[2] The potential association between NEC and recent packed red blood cell (pRBC) transfusion was first noted in a 2005 case report.[3] Single-center and multicenter retrospective analyses have identified similar associations.[4–7] A meta-analysis published in 2012 observed associations between transfusion and NEC, as well as increased risk of mortality with transfusion-associated NEC (TANEC), or NEC within 48 hours of pRBC transfusion.[8] However, a second meta-analysis expressed more caution. [9] By demonstrating an interesting, though non-significant trend towards a lower incidence of NEC in the liberal arms of three transfusion-related, randomized, controlled trials the authors highlight the tension between the inherent risk of transfusion and the apparently increased risk of transfusing in a state of severe anemia.[10–12] Finally, a small case series demonstrated decreased incidence of NEC after implementing a conservative peri-transfusion feeding protocol but had only 2 cases of NEC at all in the post-implementation phase and did not specifically measure TANEC.[13]

With the literature conflicted and our own preliminary data suggesting pre-transfusion hematocrit as a potential risk factor for TANEC, we sought to identify factors associated with developing both NEC and TANEC and to compare the incidence of TANEC before and after the introduction of a peri-transfusion feeding protocol within our institution.

Methods

We performed a retrospective cohort study of all inborn, very low birth weight (VLBW, <1500 g birth weight) infants admitted to the Duke Intensive Care Nursery between 2002 and 2010. We defined both medical and surgical NEC according to modified Bell's criteria and date of NEC as date of first pneumatosis, portal venous gas, or pneumoperitoneum.[14] If an infant was never diagnosed with pneumatosis intestinalis on radiograph but had other radiographic abnormalities and was treated with a complete ten-day antibiotic course for medical NEC, we defined date of onset as the first day of antibiotic treatment. We defined TANEC as NEC occurring with 48 hours following a pRBC transfusion.

In February 2009, the Duke Intensive Care Nursery implemented a peri-transfusion feeding protocol. The protocol specifies that oral food and fluids are to be withheld from infants for 4 hours before, during, and after transfusion, at which time feeds are restarted at 50% of the original volume for 12 hours and then advanced to the original volume. We divided the cohort into pre/post epochs using February 2009 as the division point. We then determined the pre/post protocol incidence of NEC and proportion of NEC that was TANEC. Our study

was powered to detect a 50% relative drop in overall incidence of NEC between the two epochs with >80% power.

Ten infants who developed NEC were inborn at Duke but transferred to a Duke-affiliated facility prior to being diagnosed with NEC. These infants were all transferred back to Duke Hospital for management at the time of diagnosis; however, neither transfusion nor laboratory data were uniformly available for these infants during their outside hospital stays. As a result, we were unable to evaluate their transfusion-related laboratory values. In cases where pRBC transfusion date was documented in the discharge summary (seven of the ten), we included the transfusion for analysis and defined the timing as midnight on the day of transfusion to avoid potentially over-calling the association of transfusions with NEC.

JMP Pro 10 (Cary, NC) and STATA 12.0 (College Station, TX) were used for statistical analyses. Significance was determined by ANOVA, chi-square, and logistic regression including clustering by patient to control for bias as appropriate. We also performed a multiple regression analysis including RBC unit age and pre-transfusion hematocrit to evaluate for potential interaction. This study was approved by the Duke Institutional Review Board.

Results

We identified a total of 1380 VLBW infants, of whom 148 (10.7%) developed NEC. We found a significant reduction in incidence of NEC from 126/1065 (12%) to 22/315 (7%) (P=0.01) in the pre- and post-protocol cohorts respectively (Table 1). When measured by overall incidence in the VLBW population, we found a non-significant reduction in TANEC from 51/1065 (5%) to 9/315 (3%) (P=0.16). When measured as prevalence among infants developing NEC, we found no difference in TANEC within 24, 48, or 72 hours of transfusion (Table 2). Within the NEC cohort, TANEC infants were of lower birth weight and were significantly more likely to develop surgical NEC—37/60 (62%) vs. 36/88 (41%), P=0.02 (Table 3). Finally, among just TANEC infants, transfusions given within 48 hours of NEC had a significant lower mean pre-transfusion hematocrit than all other transfusions given prior to their NEC episodes (28% vs. 33%, P<0.001).

Of the 808 transfusions received by all NEC infants, 70 (8.7%) were given within 48 hours of NEC with some TANEC infants receiving multiple pRBC transfusions during the 48-hour window. 738 transfusions were given before NEC but outside the 48-hour window. Mean pre-transfusion hematocrit was not significantly different between the pre- and post-implementation cohorts (29% vs. 29%, P=0.24). We found an inverse relationship between risk of TANEC and pre-transfusion hematocrit—OR=0.87 (95% confidence interval; 0.79–0.95). The age (days) of the pRBC unit was no different between groups (Median age of 7 days with interquartile range of 6-9 days for both TANEC and non-TANEC transfusions) and did not affect TANEC risk—OR=0.96 (0.87–1.06). We then performed multivariate regressions using pRBC unit age and pre-transfusion hematocrit as covariables on both the entire (2002–2010) cohort and separately on just the post-implementation (2009–2010) cohort. Pre-transfusion hematocrit remained associated with TANEC in all analyses (P=0.001). Finally, we attempted to categorically define the cut-point for this association

using pre-transfusion hematocrits of ≤25%, ≤27%, or ≤30%. All cut-points remained significantly associated with TANEC: OR=2.87 (1.44–5.73) for ≤25%; OR=2.70 (1.53–4.76) for ≤27%; OR=1.89 (1.10–3.26) for ≤30%.

Discussion

We demonstrated a reduction in NEC after implementing a conservative, structured peri-transfusion feeding protocol. Despite this reduction, there was no change in the proportion of NEC that was transfusion-associated. There are several possible explanations for our findings, including the major confounding factor in almost any project—concurrent changes in practice and protocol. During our 2002–2010 timeframe, our unit, along with neonatal intensive care units (NICUs) around the country, implemented other practice changes to improve overall outcomes including increased emphasis on use of human milk and use of donor milk for all VLBW infants whose mothers consented and were not producing their own milk.[15] Contemporaneously with our project, our NICU also embarked on efforts to improve antibiotic stewardship, reduce transfusion volume from 10–15 ml/kg to no more than 10 ml/kg, implement new guidelines for when to transfuse (though there was no difference in mean pre-transfusion hematocrit pre to post implementation), and implement a markedly successful effort to reduce central line infections. The significant reduction in culture-proven sepsis (Table 1) post implementation lends additional evidence to this theory, though this finding could represent both a cause of and/or an effect from our reduction in NEC.

Other authors have noted an increased risk of NEC for infants of African-American descent,[16] though center differences in both population and practice likely played a role in these studies.[17] Given this potential association, we probed the difference in racial make-up of our pre- and post-protocol populations to determine whether the change in proportion of African-American infants may have affected NEC outcomes. We found no difference in incidence of NEC or surgical NEC between infants with maternal African-American race and infants of other races, a finding that held in both the entire cohort and separately for both the pre and post cohorts (data not shown). As a retrospective cohort study we had no control over our population characteristics, but given these findings we do not believe the change in racial make-up of our cohorts significantly affects our conclusions.

Our findings are also notable in that the only other paper analyzing incidence of NEC pre/post-feeding protocol did not specifically evaluate TANEC.[13] As our study demonstrated reduced NEC but no change in TANEC, it will be important to evaluate future studies around feeding and NEC specifically with changes in TANEC. However, because the drop in overall incidence of NEC after implementation of our feeding protocol was so profound (a drop that appears to remain intact in our internal analyses post 2010) and TANEC cases were more likely to require surgical management, we are reluctant to abandon this practice. Additionally, though we are confident our prevalence of TANEC did not change, our single-center population was underpowered to detect the 2% drop in overall incidence of TANEC between our pre- and post-protocol epochs. However, we are a participating site in the Neonatal Research Network's Transfusion of Prematures (TOP) trial (NCT01702805)—a randomized, multi-center comparison of high versus low transfusion thresholds for

extremely low birth weight infants—which we expect will be powered to detect even small differences in incidence of NEC and TANEC.

The association between TANEC and surgical NEC has also been previously reported in some analyses[8] and not reported in others.[7] The heterogeneity of this finding in previous studies, as well as the lack of increased mortality in our TANEC cohort despite significantly increased surgical NEC, warrants further evaluation.

Finally, we hypothesized that pre-transfusion hematocrit and pRBC unit age may be associated with risk of TANEC. Significantly, pre-transfusion hematocrit does appear to be inversely associated with TANEC. We attempted to define a categorical cut point for this association but found association with TANEC even up to a hematocrit of ≤30%. It is interesting to note that the data Kirpalani et al. pooled from neonatology's three randomized controlled trials for transfusion thresholds also suggested a protective effect for higher hemoglobin thresholds.[9]. Our findings support the concept that transfusing pRBCs in a state of severe anemia can increase risk of NEC, potentially mediated through a combination of mucosal injury and impairment of wound healing.[18]

Though the nature of our study makes it impossible to completely separate the risk of NEC generated by anemia from the risk of the transfusion given to treat the anemia, we postulate that it is the interaction between the anemia and the transfusion that actually increases risk of NEC. Insufficient nitric oxide bioavailability (INOBA) represents a potential pathophysiologic pathway for TANEC involving S-nitrosylated (SNO) hemoglobin.[19,20] Nitric oxide (NO) appears to help regulate vasoactivity in response to local oxygen demands, and loss of S-nitrosylation has been correlated with tissue hypoxemia. Thawed packed red cells lose structural integrity and deformability, resulting in the release of sub-micron cell-free hemoglobin micro-particles that consume NO and increase blood viscosity.[21] Two reports suggest storage of red blood cells depletes SNO hemoglobin.[22,23] Thus, if transfused red cells are already stripped of their vasodilatory properties, in the face of increased local oxygen demand, the local microcirculatory response will be impaired, potentially leading to hypoxemia, ischemia, and NEC.

Though the proposed INOBA pathway physiology would suggest that older pRBC units should increase risk of NEC, previous studies, including a recent randomized, controlled trial, have not borne out this association.[5,13,24] While our study is limited in that we did not collect transfusion data on non-NEC infants, our data also demonstrate that older pRBC units do not specifically increase the risk of TANEC among infants who ultimately developed NEC. However, as in the randomized trial, we measured pRBC unit age in days while SNO hemoglobin depletion occurs in hours.[22] Furthermore, though the INOBA hypothesis may not be strengthened by our findings, our results are consistent with a disruption in normal physiology that occurs when transfusions are given in the setting of severe anemia. This disruption may involve relatively higher amounts of non-nitrosylated red blood cells reducing tissue perfusion and requires further analysis.

Our study has several limitations. As a retrospective cohort study, we are limited by the data that were collected during our analysis timeframe. Though we were able to obtain

transfusion and laboratory information for almost every infant, we still had missing data and were unable to collect other data that may have proved interesting (e.g., use of human-milk feedings, H2 blockers, and number/length of antibiotic courses). Furthermore, we were also forced to estimate transfusion time in the ten transfer infants. If anything, our chosen methodology should have negatively affected our effect size as most transfusions were more likely to occur during daylight hours. Removing these ten infants entirely from the dataset made no difference in the pre/post analysis for TANEC. It is also possible that feeding practices varied within our unit and the two Duke-affiliated outside nurseries, though neonatologists within our division who would be responsible for implementing any changes in protocol staffed all three units during the study's entire timeframe. Additionally, given transit times of over 24 hours it is unlikely that holding feeds for 4 hours prior to a transfusion is long enough for a premature infant's intestines to fully clear. Finally it is possible, though unlikely, that our group's neonatologists either held feeds or continued feeds during pRBC transfusion despite the change in feeding protocols. If anything, this would have further biased our hypothesis towards the null, as members of our group who helped write the new protocol may have begun holding feeds during transfusion prior to the protocol's implementation date.

Though the prevalence of NEC among VLBW infants fell significantly within our single-center population after introducing a novel peri-transfusion feeding protocol, we found no difference in TANEC. TANEC infants were smaller and more likely to develop surgical NEC than other infants who developed NEC, suggesting that careful consideration be given when transfusing our smallest patients. However, risk of TANEC was inversely related to pre-transfusion hematocrit, suggesting higher transfusion thresholds may be protective. We anticipate the Neonatal Research Network's Transfusions of Prematures trial (NCT01702805) and other multicenter, randomized, controlled trials will better quantify these associations and ultimately lead to better evidence-based transfusion thresholds for VLBW infants. Additionally, other methods of avoiding low hemoglobin at critical times during the course of at-risk infants – e.g., stimulating erythropoiesis, maintaining adequate iron stores, and reducing blood draws – may warrant further investigation as well.

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Table 1

Subject demographics

	Pre-protocol (2002–08), Mean (5th–95th percentile) or n (%), N = 1065	Post-protocol (2009–10), Mean (5th–95th percentile) or n (%), N = 315	P
Birth weight (g)	1012 (540–1460)	1042 (558–1480)	0.12
Gestational age (weeks)	28 (23–32)	28 (24–33)	0.18
Female	530 (50)	156 (50)	0.94
African-American	575 (54)	143 (45)	<0.01
NEC	126 (12)	22 (7)	0.01
TANEC	51 (5)	9 (3)	0.16
Surgical NEC	61 (6)	12 (4)	0.60
Culture-proven sepsis	249 (23)	52 (17)	<0.01
Death	133 (13)	31 (10)	0.19

NEC, necrotizing enterocolitis.

TANEC, transfusion-associated necrotizing enterocolitis (48 hour window)

Table 2

Proportion of NEC episodes preceded by pRBC transfusion

NEC	Pre-feeding protocol, n (%), N=126	Post-feeding protocol, n (%), N=22	P
pRBC transfusion within 24 hours	28 (22)	7 (32)	0.41
pRBC transfusion within 48 hours	51 (41)	9 (41)	>0.99
pRBC transfusion within 72 hours	62 (49)	10 (45)	0.82

NEC, necrotizing enterocolitis; pRBC, packed red blood cell.

Table 3

Comparison of infants with TANEC and infants with non-TANEC

	TANEC, Mean (5th–95th percentile) or n (%), N=60	Non-TANEC, Mean (5th–95th percentile) or n (%), N=88	P
Birth weight (g)	817 (498–1218)	895 (560–1400)	0.049
Gestational age (weeks)	26 (23–29.5)	27 (23–31)	0.06
Female	22 (37)	43 (51)	0.18
African-American	26 (55)	50 (57)	0.87
Surgical NEC	37 (62)	36 (41)	0.02
Age at time of NEC (days)	35 (7–80)	35 (6–73)	>0.99
Culture-proven sepsis	28 (47)	36 (41)	0.50
Death	20 (33)	20 (23)	0.19

NEC, necrotizing enterocolitis; TANEC, transfusion-associated necrotizing enterocolitis.