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Feeding practices and other risk factors for developing transfusion-associated necrotizing enterocolitis

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ABSTRACT

Aims: The objective of this study is to 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 to 2010. We defined NEC using Bell's modified criteria IIA and higher and TANEC as NEC occurring within 48 h 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).
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 that other unmeasured interventions may account for the observed decreased incidence of NEC.

1. 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 h 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 potentially 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

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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.

2. 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 h 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 h before, during, and after transfusion, at which time feeds are restarted at 50% of the original volume for 12 h 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.

3. 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 h 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 h 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 h of NEC with some TANEC infants receiving multiple pRBC transfusions during the 48-h window. 738 transfusions were given before NEC but outside the 48-h 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%.

Table 1
Subject demographics.

	Pre-protocol (2002–2008), Mean (5th–95th percentile) or *n* (%), *N* = 1065	Post-protocol (2009–2010), 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 (within 48 h 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 h	28 (22)	7 (32)	0.41
pRBC transfusion within 48 h	51 (41)	9 (41)	>0.99
pRBC transfusion within 72 h	62 (49)	10 (45)	0.82

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

4. 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

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.