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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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 previous studies and suggest that the association between NEC and transfusion may be contextual. *(J Pediatr 2014;165:678-82)*.

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

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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The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.06.012

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 nonevents 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