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Association between Red Cell Transfusions and Necrotizing Enterocolitis

Sachin C. Amin^{1,2}, Juan I. Remon^{1,2}, Girish C. Subbarao³, and Akhil Maheshwari^{1,2,4}

¹Department of Pediatrics Division of Neonatology, University of Illinois at Chicago, 840 S Wood St, CSB 1257, Chicago, IL 60612

²Department of Pediatrics Center for Neonatal and Pediatric Gastrointestinal Disease, University of Illinois at Chicago, 840 S Wood St, CSB 1257, Chicago, IL 60612

³Department of Pediatrics (Division of Pediatric Gastroenterology, Hepatology, and Nutrition), Riley Hospital for Children at IU Health, 705 Riley Hospital Dr, ROC 4210, Indianapolis, IN 46202

⁴Department of Pharmacology, University of Illinois at Chicago, 840 S Wood St, CSB 1257, Chicago, IL 60612

Abstract

Several case reports and retrospective studies have reported a temporal association between RBC transfusions and necrotizing enterocolitis. In this article, we summarize the clinical evidence and biological plausibility of the association between RBC transfusions and NEC. We also review the clinical presentation, management, and outcomes in infants with “transfusion-associated” NEC.

Keywords

NEC; anemia; transfusion; RBC; intestinal injury

Premature infants are a heavily-transfused population, with more than half of all very low birth weight infants (VLBW) infants receiving one or more red blood cell (RBC) transfusions during their hospital stay (1). In recent years, there has been renewed interest in potential adverse events following the administration of blood products, particularly in the context of the reported association between RBC transfusions and necrotizing enterocolitis (NEC) (2, 3). Several case reports and retrospective studies show that up to a third of all VLBW infants who develop NEC may have received one or more RBC transfusions in the preceding 24-72 hours prior to onset of NEC (4-18). In this article, we evaluate the quality of evidence and biological plausibility of this association, and review the clinical presentation and management of “transfusion-associated” NEC.

Address for correspondence: Akhil Maheshwari, MD, 840 S Wood St, CSB 1257, UIC m/c 856, Chicago, IL 60612, Phone: 312-996-4185; Fax: 312-355-5548, akhil1@uic.edu.

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Do RBC transfusions cause NEC in premature infants?

Increasing clinical evidence indicates that the answer to this question may be in the affirmative, although causality is yet to be demonstrated. The association between RBC transfusions and NEC was first noted by McGrady *et al.* in 1987, who investigated an outbreak of 33 cases of NEC in their neonatal intensive care unit (NICU) and reported that RBC transfusions increased the risk of NEC (odds ratio 15.1, confidence interval (CI) 2.59-92.51). In 1998, Bednarek *et al.* (6) compared transfusion practices in VLBW infants in six NICUs and in multivariate analysis, noted that NICUs with fewer transfusions had a lower incidence of NEC (adjusted odds ratio 0.3, CI 0.1-0.8) than in those with a larger number of transfusions (odds ratio 1.1, CI 0.5-2.2). Since then, sporadic cases of “transfusion-associated” NEC continued to be recognized by clinicians, as exemplified by the case reports by Agwu and Narchi (19), and Short *et al.* (20).

In recent years, the association between RBC transfusions and NEC has received significant investigative attention. Since 2006, several retrospective studies led by Mally (14), Perciaccante (21), Holder (18), Christensen (5), Josephson (7), Carter (8), Couselo (9), Paul (10), Singh (11), El-Dib (12), Blau (13), Ghirardello (15), Stritzke (16), and Wan-Huen (17) have been published. Although these study cohorts show important differences in demographics, severity of illness, age of RBCs, and the baseline incidence of NEC, several common elements are seen (Table 1): (a) of all the cases of NEC, 25-40% may have received an RBC transfusion in the preceding 2-48 hours, generally about 12 hours, prior to onset of NEC (4-18); (b) neonates with transfusion-associated NEC are generally born at an earlier gestation than those who develop NEC unrelated to transfusion (4-18); (c) transfusion-associated NEC has a delayed onset at 3-5 weeks of postnatal age, whereas those with NEC unrelated to transfusion are generally younger (1-3 weeks old) (4-11, 13-18); (d) neonates with transfusion-associated NEC have had one or more previous RBC transfusions (5, 10); and (e) the age of the blood transfused (days since donor draw) does not differ significantly between those with transfusion-associated NEC, those who developed NEC without a history of a temporally-proximate transfusion, and matched controls who underwent transfusion but did not develop NEC (5, 7, 10); (f) infants who developed NEC following a transfusion may have had a higher acuity of illness with higher odds of having had a patent ductus arteriosus (pooled odds ratio 2.68, CI 1.81–3.97) (7, 13, 14, 16, 18, 22) and of being ventilated at the time of diagnosis (pooled odds ratio 3.16, CI 1.60–6.22) (7, 12-14, 18, 22).

In contrast to the other studies, Harsono *et al.* (23) detected a protective effect of RBC transfusions against NEC. They reviewed the clinical course of 2123 infants (birth weight $966g \pm 265$ grams) to investigate whether VLBW infants who receive RBC transfusions beyond postnatal age of 28 days were at increased risk of NEC in a 48 hour period following the transfusion. In their cohort, 43 (2%) infants developed NEC beyond postnatal day 28, and 26 of these 43 infants (60%) developed NEC within 48 hours of receiving a blood transfusion. After controlling for birth weight, gender, and a history of umbilical artery catheter insertion, infants who received a transfusion were less likely to develop NEC than those who did not receive a blood transfusion (OR= 0.30; 95% CI: 0.15-0.60). The

authors concluded that RBC transfusions may protect against 'late-onset' NEC by reducing the effects of chronic anemia and consequent tissue hypoxia.

Mohamed and Shah (22) recently published a meta-analysis of observational data from studies on transfusion-associated NEC. They confirmed increased odds of NEC within a 48-hour period following an RBC transfusion. Meta-analysis on 5 studies that reported unadjusted estimates of exposure to transfusion in previous 48 hours and NEC (5, 10-12, 21) showed increased odds of NEC after recent transfusion (pooled odds ratio 3.91, CI: 2.97–5.14; $I^2 = 58\%$). Meta-analysis of 4 studies (10, 16, 17, 23) that reported adjusted estimates revealed a similar but lower risk of NEC (pooled adjusted odds ratio 2.01, CI: 1.61–2.50; $I^2 = 91\%$). Exclusion of Harsono *et al.* (23) from meta-analysis led to disappearance of statistical heterogeneity (pooled odds ratio 2.48, CI: 1.97–3.12, $I^2 = 0$).

Can RBC transfusions cause NEC in premature infants?

Although transfusion-associated NEC has no proven pathogenic mechanism, several plausible explanations have been proposed. These include immaturity of the splanchnic vascular bed, immune mechanisms similar to those seen in transfusion-related acute lung injury (TRALI), re-oxygenation injury in the anemic gut, and the effects of stored RBCs.

Host immaturity

Several studies had demonstrated immaturity of the vascular autoregulatory responses in the neonatal gastrointestinal tract, potentially placing the infant at increased risk of gut mucosal injury. Using newborn piglets, Szabo *et al.* (24) showed that hypoxia impaired the normal post-prandial hyperemic response, decreased arterial oxygen content and gut oxygen delivery, but at the same time, increased tissue oxygen extraction. In the clinical setting, Krimmel *et al.* (25) showed that RBC transfusions can dampen the normal postprandial increase in mesenteric blood flow in premature infants, particularly in those with a birth weight <1250 grams. In another study, Gupta *et al.* (26) demonstrated that RBC transfusions in infants with a hemodynamically-significant *ductus arteriosus* were associated with reduced mesenteric blood flow 4 hours after completion of the transfusion. Besides physiological immaturity of the splanchnic vascular bed in the preterm infant, Blau *et al.* (13) suggest that there may be additional biological reasons to explain the occurrence of transfusion-associated NEC at approximately 31 weeks of post-menstrual age (PMA). They note that this specific PMA coincides with various conditions associated with neovascularization and oxygen toxicity, and speculate that the expression of angiogenic factors (such as the vascular endothelial growth factor) in the anemic gastrointestinal tract may be subject to similar developmental irregularities as in the retina in infants with severe anemia (27).

Transfusion-related acute gut injury?

Blau *et al.* (13) hypothesized that transfusion-associated NEC may also share immunological mechanisms with TRALI. TRALI is speculated to result in a two-hit model in which host neutrophils are primed by an antecedent illness, followed by passive transfusion of biological response mediators such as donor antibodies such as those directed

against the human leukocyte antigens (HLA), biologically-active lipids, free hemoglobin, red cell membrane fragments, and inflammatory cytokines present in stored blood (28). Similar factors may cause mucosal injury in the premature intestine, which displays a developmentally-regulated pro-inflammatory bias with exaggerated immune responses to bacterial and/or nutritional antigens (29, 30). Anti-HLA antibodies have been detected in some (31), but not all (13), studies on premature infants who were transfused and developed NEC. Paul *et al.* (10) reported that 83% donors in their cases of transfusion-associated NEC were male, who were less likely to carry anti-HLA antibodies in their blood than female donors. Another mechanistic consideration would invoke the presence of free hemoglobin (resulting from RBC lysis during storage and/or washing), interacting with additional humoral mediator(s) introduced via plasma (28).

Anemia

Studies in animal models demonstrate that anemia can impair splanchnic perfusion and increase oxygen extraction as a compensatory mechanism (24), which may lead to anaerobic metabolism and accumulation of its by-products such as lactic acid (32). Intestinal vascular resistance changes rapidly during transition from fetal to early neonatal life. Anemia can impair this normal transition (33), predisposing the developing intestine to hypoxic-ischemic gut mucosal injury, and possibly, to NEC (32). In a recent study, Singh *et al.* (11) investigated the association between anemia and transfusion-associated NEC in a cohort of 111 preterm infants with confirmed NEC and 222 matched controls. In a multivariate model, lower hematocrit was associated with increased odds of NEC (odds ratio 1.10, $p=0.01$) after controlling for other factors. They showed that RBC transfusions had a temporal relationship with onset of NEC, where a transfusion within the preceding 24 hours (odds ratio 7.60, $p=0.001$) and 48 hours (odds ratio 5.55, $p=0.001$) was associated with increased odds of developing NEC. This association was no longer significant by 96 hours post-transfusion. However, in contrast to this study, the relationship between the severity of the underlying anemia and risk of transfusion-related NEC was not evident in other studies, including our own (7), and those by Christensen *et al.* (5), Paul *et al.* (10), and Blau *et al.* (13).

In convalescing preterm infants, the most likely reason for a low hematocrit beyond 3-4 weeks of postnatal age is anemia of prematurity. However, in infants with NEC, other etiologies may need to be carefully excluded. Some studies have shown an association of NEC with activation of the Thomsen-Friedenreich cryptic T antigen (T-antigen activation) on RBCs, causing low-grade hemolysis and anemia in multi-transfused patients who have previously received blood from adult donors carrying anti-T antibodies (34). Although the pathophysiological significance of T-activation in NEC remains unresolved (35), the presence of low-grade smoldering NEC prior to transfusion may be difficult to exclude in some patients. Growing preterm infants who are anemic but otherwise stable are usually monitored with an expectation of spontaneous improvement in hematocrits. Because anemia could manifest in premature infants with myriad presentations (36), non-specific symptoms of early NEC such as tachycardia, feeding intolerance, and irritability could be ascribed to anemia and treated with a transfusion. In these infants, later development of more obvious clinical manifestations of NEC could easily be associated erroneously with the RBC transfusion.

Stored blood

Stored RBCs show well-known 'storage lesions' such as reduced deformability, increased RBC adhesion and aggregation, and the loss of nitric oxide. Nitric oxide stored in RBCs is covalently-bound to cysteine residues of hemoglobin and its gradual release helps maintain microvascular perfusion and tissue oxygen delivery. In stored blood, RBCs are rapidly depleted of nitric oxide, which correlates with loss of RBC function, and can be associated with a paradoxical reduction in oxygen delivery, vasoconstriction, and ischemic injury to the intestine (and other organs) (37). Stored RBCs may also have direct pro-inflammatory effects such as activation of neutrophils to produce interleukin (IL)-8 and phospholipase A2. Transfused blood contains high levels of IL-1, IL-6 and IL-8, which may rise further with increasing duration in storage (38).

Is there merit in withholding feeds around the time of transfusion?

So far, two studies have addressed the issue of withholding feeds around the time of transfusion (12, 21). After a cluster of cases of transfusion-associated NEC, Perciaccante *et al.* (21) changed from a practice of no disruption of feeding schedules to a practice of withholding feedings from 4 hours before the start of the transfusion until 4 hours after the completion of the transfusion. Before introducing the practice of withholding feedings, they recorded a history of an RBC transfusion in the preceding 48 hours prior to onset of NEC in 7 out of 18 (38.9%) cases of NEC. Following the change in feeding practices, they did not record any cases of NEC that occurred within 48 hrs of an RBC transfusion. These findings are similar to those reported by El-Dib *et al.* (12), who also changed their feeding policy in the second half of their study and detected a significant reduction in the incidence of transfusion-associated NEC from 5.3% to 1.3% after instituting the policy change.

Do infants with transfusion-associated NEC fare worse than other cases of NEC?

In our own study (7), infants with transfusion-associated NEC had a higher frequency of surgical intervention and longer duration of stay than those with non-transfusion-associated NEC. The overall mortality in NEC/RBC-transfused and NEC/non-RBC-transfused groups was similar (10/47, 21% vs. 7/46, 15%, respectively; $p=0.45$). These results contrast with the findings of Stritzke *et al.* (16), who reported mortality and morbidity data from a large cohort of VLBW infants from Canadian Neonatal network. After adjusting for confounding factors, no significant differences in mortality/neonatal morbidity were found between the two groups. Of all the studies on transfusion-associated NEC, six (5, 12, 13, 16, 18, 21) have reported unadjusted estimates of mortality. Meta-analysis of these studies (22) revealed higher odds of mortality in patients who had transfusion-associated NEC compared with those with NEC not associated with transfusion (pooled odds ratio 1.88, CI 1.35–2.61). None of the studies have reported adjusted estimates.

Clinical outcomes in transfusion-associated NEC need careful evaluation because these infants were more premature and may have had a higher severity of illness prior to and at the time of transfusion (5, 7-13, 15-17, 21), both of which are independent predictors of

morbidity and mortality in NEC (29). In our study (7), patients who developed NEC and had received one or more transfusions also had a higher incidence of PDA, a higher frequency of intraventricular hemorrhage, and more frequent use of central vascular catheters. In our own study (7), and in several others (12, 13, 18), infants who developed NEC after a transfusion were more likely to be on respiratory support (supplemental oxygen/assisted ventilation) in a 48 hour-period preceding the onset of NEC.

Conclusion

Based on current clinical evidence, transfusion-associated NEC appears to be a plausible clinical entity. However, there is a need for cautious interpretation of data because all the studies that have been conducted until date are retrospective, and therefore, susceptible to bias and to the effect of confounding variables (39). A large, prospective, multi-center trial is needed to evaluate the association between RBC transfusion and NEC, clinical characteristics of transfusion-associated NEC, outcomes, and the scientific merit of interventions such as withholding feeds before and during PRBC transfusion. Strategies to decrease RBC transfusions, such as the use of recombinant erythropoietin or its synthetic, longer-acting homologues such as darbepoietin may also be of interest. Other potential approaches include repletion of nitric oxide in stored RBCs before transfusion or administration of inhaled nitric oxide to at-risk neonates during transfusion (5).

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Table 1
Published studies (excluding abstracts) designed to investigate the association between RBC transfusions and NEC

	Mally 2006	Holder 2009	Christensen 2010	Josephson 2010	El-Dib 2011	Paul 2011	Blau 2011	Singh 2011	Stritzke 2012	Ghirardello 2012
Study Design	Case-Control	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control	Case Control
Total NEC	17(1.8%)	5.8%	112	93 (2.5%)	25(3.3%)	122 (5.3%)	35 (14%)	111	927 (1.6%)	30 (5.5%)
NEC with RBC Transfusion	6	7		47	14	92	24		144	4
NEC associated with proximate RBC transfusions	35%	NA	35%	38.3%	Greater percentage of NEC patients received TX within 48 hrs. ($p=0.019$)	35.9%	37.5%	Increased odds of NEC within 24 hrs and 48 hrs	Increased odds of NEC within 2 days OR 2.44 (1.87-3.18)	13.3%
NEC not associated with RBC transfusion	11	30	72	46	11	30	12	NA	783	26
Gestational age (weeks) Transfusion associated NEC vs. NEC not associated with transfusion.	NS	25 vs. 28	27 vs. 30	25.9 vs. 30.7	NS	26.8 vs.28.6	26 vs.29	NA	25.8 vs. 29.3	25 vs.33
Birth weight (grams) Transfusion associated NEC vs. NEC not associated with transfusion	845 vs. 930	666 vs. 1277	981 vs. 1371	760 vs. 1415	NS	969 vs. 1109	770 vs. 1114	NA	885 vs. 1373	725 vs.1804
Postnatal age (days) Transfusion associated NEC vs. NEC not associated with transfusion	32 vs. 12	NS	23 vs. 16	37 vs. 13	21 vs. 38(NS)	29.5 vs. 13.9	30 vs.14	NA	20 vs. 14	29 vs.13
Hematocrit prior to NEC Transfusion associated NEC vs. NEC not associated with transfusion	24 vs. 37	NS	NA	29.6 vs. 34.1	NA	NA	26 vs. 38	NA	Transfusion-associated NEC correlated with decreasing hematocrit	30.3 vs.45.1
Feedings Transfusion associated NEC vs. NEC not associated with transfusion	NA	Full oral feeds 43% vs. 70%	115 ml/kg/day vs. 16 ml/kg/day (24 hours prior to NEC) NEC vs. controls	NS	NS In phase 2 of trial, policy change to make NPO during transfusion NEC decreased from 5.3% to	NS	NS	NA	NA	NA

	Mally 2006	Holder 2009	Christensen 2010	Josephson 2010	El-Dib 2011	Paul 2011	Blau 2011	Singh 2011	Stritzke 2012	Ghirardello 2012
Mechanical Ventilation Transfusion associated NEC vs. NEC not associated with transfusion	0 vs. 45%	86% vs. 46%	NA	76% vs. 24%	1.3% (<i>p</i> =0.047) NS	NA	NA	NA	NA	NA
Age of transfused RBCS (days) Transfusion associated NEC vs. NEC not associated with transfusion	12+/-10 vs. 6 +/- 4	NA	NS	9 vs. 8	NS	NS	NA	NA	NA	NA

Abbreviations: NA = information not available; NS = data not significant; vs. = versus; NEC = necrotizing enterocolitis; RBC = red blood cell