Feeding Preterm Infants during Red Blood Cell Transfusion Is Associated with a Decline in Postprandial Mesenteric Oxygenation

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Objective To evaluate the mesenteric tissue oxygenation response in preterm infants fed and not fed during red blood cell (RBC) transfusions.

Study design Prospective, observational comparison of mesenteric oxygenation using near-infrared spectroscopy in preterm infants (<33 weeks' at birth) who were fed or not fed during RBC transfusion. Tissue oxygenation means were examined up to 48 hours after each transfusion event.

Results Mean mesenteric regional oxygen saturation (rSO_2) slopes during RBC transfusion of fed (n = 9) vs not fed (n = 8) infants ranged from −0.23 to +0.23 (mean 0.04) with no differences between groups ($P = .480$). However, following transfusions, postprandial mesenteric oxygenation means significantly declined in infants fed during transfusion compared with infants not fed during transfusion ($P < .001$). Infants fed during RBC transfusion had a mean 2.16 point decrease in rSO_2 mesenteric oxygenation with each sequential feeding post-transfusion, whereas infants not fed during RBC transfusion increased their rSO_2 postprandial mesenteric oxygenation by a mean of 2.09 points.

Conclusions Mesenteric tissue oxygenation during RBC transfusion is not influenced by feeding status. However, infants fed during RBC transfusion had, for the next 15 hours, decreasing postprandial mesenteric tissue oxygenation patterns compared with infants not fed during RBC transfusion. Feeding during RBC transfusions may increase the risk for mesenteric ischemia and the development of transfusion-related necrotizing enterocolitis in preterm infants. *(J Pediatr 2014;165:464-71)*.

Necrotizing enterocolitis (NEC) is a disease likely attributable to multiple factors and characterized by intestinal ischemia, inflammation, and necrosis.[1] NEC occurs in up to 10% of very low birth weight (VLBW <1500 g) infants and is associated with a mortality rate between 30% and 50% for those requiring surgical intervention.[2] Survivors have substantial morbidities including long-term feeding difficulty and neurodevelopmental delay.[3,4] Recently, red blood cell (RBC) transfusions were linked to the development of NEC in premature infants, which we have termed transfusion-related NEC (TR-NEC), similar to the terminology found in the literature such as transfusion-associated NEC,[5-9] transfusion-related acute gut injury,[10] and transfusion-related acute mesenteric injury.[11] Previous studies have shown that up to one-third of VLBW infants who developed NEC were transfused within 48 hours prior to the onset of symptoms.[12-14] Although the pathogenesis of TR-NEC is unclear, one hypothesis proposes enteral feeding during RBC transfusion may alter intestinal circulation predisposing tissues to ischemia.[15,16] Studies using near-infrared spectroscopy (NIRS) demonstrate that in stable, nontransfused growing preterm infants, mesenteric oxygenation increases during enteral feedings.[17,18] In contrast, Doppler studies indicate that superior mesenteric artery blood flow does not increase after RBC transfusions, and the increase in superior mesenteric artery flow after feeding is eliminated immediately following a transfusion.[19] Currently, there are no prospective data evaluating the impact of enteral feeds during and subsequent to RBC transfusion on mesenteric tissue bed oxygenation. The current study used NIRS to evaluate the regional mesenteric tissue oxygenation saturation response in preterm infants who were enterally fed during RBC transfusion compared with those who were not fed during RBC transfusion.

MLM	Multilevel linear model
NEC	Necrotizing enterocolitis
NIRS	Near-infrared spectroscopy
NO	Nitric oxide
PMA	Postmenstrual age
PNA	Postnatal age
RBC	Red blood cell
rSO_2	Regional oxygen saturation
TR-NEC	Transfusion-related NEC
VLBW	Very low birth weight

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Methods

This institutional review board-approved prospective, observational study recruited preterm infants (<33 weeks' gestational age at birth) admitted to the Emory University Midtown Level IIIB neonatal intensive care unit from November 30, 2010, to December 31, 2011. Preterm infants were recruited if they were to receive a RBC transfusion and were hemodynamically stable. Neonates with congenital anomalies, intraventricular hemorrhage grade III or greater, hemodynamically significant patent ductus arteriosus, requiring vasopressor support, and current or previous NEC diagnosis were excluded. Mesenteric tissue oxygenation values measured with NIRS technology were examined during and up to 48 hours following RBC transfusion. All infants were followed until transfer, discharge, or death for the development of NEC. Attending physician assigned NEC diagnosis based on Bell staging criteria.[20] TR-NEC was defined as a diagnosis of Bell stage NEC IA or greater within 48 hours after RBC transfusion. Birth weight, gestational age at birth, current weight, postnatal age (PNA), postmenstrual age (PMA), hematocrit, current volume and type of enteral feeds, amount/type of supplemental oxygen (fraction of inspired oxygen), and current diagnoses were recorded for each infant at the time of each RBC transfusion.

RBC Transfusion and Enteral Feeding Data

RBC transfusion (volume and duration) and enteral feeding (continuation or cessation) during the transfusion event was determined by the attending physician independent of this study. No formal protocol for RBC dose or duration, or enteral feeding continuation or cessation during RBC administration was in place. Infant hematocrit values were measured per routine neonatal intensive care policy prior to all RBC transfusions. Volume and duration of the study RBC transfusion was recorded for each infant, as were type, volume, duration, route, frequency, tolerance, and timing of enteral feeding events related to each transfusion event.

A transfusion event consisted of the RBC transfusion followed by a monitoring period of up to 48 hours. Infants received either a full (15-20 mL/kg) or 2 equally divided (7.5-10 mL/kg) transfusions separated by 12 hours. Volume of transfusion was decided by the attending physician based on individual practice. If feedings were held for an infant receiving a divided dose, the infant also did not receive feedings between RBC doses (a period of 12 hours). All transfusions were administered over 3-4 hours. NIRS monitoring for infants receiving a divided transfusion dose occurred during each dose (first and second), between doses (12 hours), and for 48 hours following completion of second dose. Full dose transfusion events were monitored during and for 48 hours following the completion of RBC transfusion. All transfusion events were grouped by feeding status: fed or not fed during RBC transfusion administration.

NIRS Data Collection

Mesenteric regional oxygen saturation (rSO_2) values were measured using a Food and Drug Administration-approved NIRS somatic oximeter (INVOS 5100C; Covidien, Boulder, Colorado). NIRS measures an rSO_2 value ranging from 15%-95%, which reflects total oxygen bound to hemoglobin. The measured value is the result of the amount of oxygen delivered minus oxygen consumed at the tissue level, reflecting tissue oxygenation.[21] Data were recorded every 30 seconds in real time before, during, and up to 48 hours after each RBC transfusion event. NIRS sensor probes were placed on the infant midabdomen, below the umbilicus for the mesenteric readings.

Statistical Analyses

Using SPSS v 21.0 MIXED procedure (SPSS Inc, Armonk, New York) descriptive statistics (mean, SD, median and range for continuous measures, sample size, and percentages for categorical variables) were analyzed for infant demographics and clinical measures specific to each transfusion event. Differences between fed or not fed groups for transfusion specific measures were analyzed using *t* tests, Mann-Whitney tests (for non-normal distributions), and Fisher exact tests (for categorical responses with expected values <5).

For each transfusion event, raw mesenteric rSO_2 measurements collected in 30-second intervals were analyzed over time in 3 phases: (1) during RBC transfusion; (2) immediately after but before first feeding after transfusion (elapsed time from end of transfusion to time of first feeding after transfusion); and (3) for each subsequent feeding after transfusion for the remainder of the monitoring period. For phases 1 and 2, the average change (slope) in rSO_2 levels across that phase's time period were calculated for each transfusion event. The slopes calculated for these first 2 phases of each transfusion were compared between fed vs not fed groups using *t* tests. Whereas, for the third phase, because of high variability in mesenteric readings, mesenteric means were calculated for each feeding occurring after RBC transfusion completion from 30-second raw rSO_2 values over a 10-minute window at 3 time points: 0 minutes (at the beginning of the feeding averaged from 5 minutes immediately prior to feeding initiation through 5 minutes into the feeding event), 30 minutes after feeding (averaged from 25-35 minutes), and 60 minutes after feeding (averaged from 55-65 minutes). We then compared rSO_2 mean changes (using change scores) from 0-30 minutes and from 30-60 minutes to capture any possible postprandial hyperemic effect. The mesenteric rSO_2 means at the beginning of the feeding and the change scores from 0-30 minutes and 30-60 minutes were then analyzed for significant trends over time (positive or negative slope) relative to whether the infant was fed or not during the RBC transfusion. To test for significant trends (slopes) in mesenteric means over time (defined by sequential feedings after transfusion) (as well as for the 2 change scores for hyperemia), 2-level multilevel linear models (MLMs) were used (using SPSS v 21.0 MIXED procedure,