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ARTICLE

# Feeding during transfusion and the risk of necrotizing enterocolitis in preterm infants

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## Abstract

**Objective** To evaluate the effect of withholding feeds during transfusion on transfusion associated acute gut injury (TRAGI).

**Study design** Data were collected on 125 preterm infants before and after the practice of withholding feeds for 12–24 h during transfusion was instituted. Logistic regression was used to examine effects of withholding feeds on TRAGI rates.

**Results** A total of 19 (15%) infants developed NEC; 6/19 (32%) had TRAGI. Postnatal hydrocortisone use was associated with TRAGI (OR 8.97; 95% CI 1.17–68.46, $p = 0.034$). There was no difference in NEC rates (15.8 vs. 14.7%) and the proportions (22.2 vs. 40%) of TRAGI in the two time periods before and after instituting the standardized feeding regimen and practice of holding feeds during transfusion.

**Conclusion** No significant decrease was noted in the rates of TRAGI after feeds were withheld during transfusion. Further studies are warranted to explore the relationship between feeds during transfusion and NEC.

## Introduction

Necrotizing enterocolitis (NEC) remains one of the most common neonatal morbidities with an incidence of about 9% and mortality rates of 20–30% in extremely preterm infants [1, 2]. Various pathophysiological pathways have been proposed for the development of NEC; the exact mechanism still remains elusive. Variation in feeding practices has been reported to contribute to higher incidence of NEC; institution of standardized feeding regimen helped to reduce the risk of NEC in a meta-analysis by Jasani et al. [3]. There has been a recent controversy about the association between packed red blood cell (pRBC) transfusion and development of acute gut injury with clinical manifestations similar to NEC. Many retrospective and observational studies have shown an association [4–12] whereas others have failed to do so [13, 14].The interaction between transfusion and gut injury known as transfusion associated gut injury (TRAGI) or transfusion associated NEC (TANEC) described in these studies tend to have more severe course with higher risk of mortality compared to NEC cases not associated with transfusion [4, 5, 11].

Reperfusion injury caused by transfusion in a hypoxic gut has been speculated as one of the pathogenic mechanisms of TRAGI. Feeding an infant during transfusion can aggravate this insult by further increasing the oxygen demand [15]. Recently, few studies have investigated the effects of withholding enteral feeds during transfusion on the risk of TRAGI [16–18] with inconsistent results. Our institution adopted standardized feeding guidelines including withholding feeding for 12–24 h during and after red blood cell transfusion in infants weighing less than 1250 g at birth in February, 2012.

The purpose of our current study was twofold: first to determine the characteristics associated with TRAGI, defined as development of NEC within 48 h of a red blood cell transfusion and secondly to evaluate the effect of a feeding regimen which included holding feeds during transfusion on TRAGI rates.

## Methods

We conducted a retrospective chart review of preterm infants with birth weight <1250 g who survived beyond 1 week of

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age over a 2 year convenience period in a single center before and after institution of standardized feeding regimen. Infants with incomplete record of feedings were excluded. The standardized regimen emphasized breast milk feeds, early initiation of trophic feeds, consistent slow advance of feeds and holding feeds for 12–24 h during and after blood transfusion. The decision to transfuse pRBC's was guided by an evidence-based institutional policy adopted from the National Institute of Child Health and Human Development Neonatal Research Network multicenter randomized control trial on the effect of erythropoietin on transfusion requirement in preterm infants that takes into consideration the extent of respiratory support, severity of anemia and symptoms [19]. Erythropoietin is not used at our institution for neonatal anemia. At our institution, pRBCS are preserved in citrate-phosphate-dextrose-adenine (CPDA-1) storage medium for a maximum of 35 days. PRBC's aliquoted from the same donor are dispensed to a single patient for duration of 1 month to minimize exposure to multiple donors. The study was approved by the Human Investigation Committee of Wayne State University. Waiver of consent was granted for this study.

Data on maternal and infant demographics and perinatal characteristics were collected. Grades 3 or 4 intraventricular hemorrhage was defined using Papile's classification on a cranial ultrasound [20], early onset sepsis defined as positive culture within 72 h of birth, culture proven late onset sepsis after 72 h of life, and bronchopulmonary dysplasia (BPD) defined as use of supplemental oxygen at 36 weeks postmenstrual age. We also collected data on patent ductus arteriosus (PDA) confirmed by echocardiogram and use of indomethacin or ibuprofen for its treatment. Data on the postnatal use of hydrocortisone for any indication was also collected. Data on age of initiation of feeds, type of feeds (breast milk/formula), number of days on parenteral nutrition, time to full feeds, central line days and nil-per-os (NPO) days were collected. NEC was defined according to modified Bell's criteria [21]. Infants with Bell's stage IIa or above were included in the study. TRAGI was defined as NEC within 48 h of red blood cell transfusion. The day of initiation of antibiotics was considered as the day of onset of NEC.

Data were collected for each pRBC transfusion till 40 weeks post menstrual age and included the days after birth and post-menstrual age at transfusion, hemoglobin and hematocrit before and after transfusion, respiratory support at the time of transfusion, blood stream infection (BSI) or hypotension requiring vasopressors within 24 h of transfusion, volume and type of feeds before and after transfusion, duration of time for which feeds were held, time to reach pre transfusion volume of feeds and development of TANEC. If there was more than one transfusion in 24 h, only the first transfusion was included.

## Statistical analyses

The entire cohort was divided into three groups: Infants who never developed NEC (no NEC), infants who developed NEC but not within 48 h of transfusion (NEC excluding TRAGI) and infants who developed NEC within 48 h of transfusion (TRAGI). Maternal and neonatal characteristics and neonatal outcomes were compared in the three groups using chi-square test for categorical variables and ANOVA for continuous variables with a posthoc Bonferroni test to compare between-group differences. A generalized logistic regression model was used to explore associations with NEC and TRAGI, adjusting for GA, antenatal steroids, antibiotic use, and variables found to be significantly different between groups.

Further analysis of data related to pRBC transfusions was carried out. PRBC transfusions were categorized as Group 1-transfusions prior to the introduction of the feeding regimen and Group 2-transfusions following the feeding regimen in which infants were made NPO for total duration exceeding 12 h. Clinical data were compared between the groups and binary logistic regression analyses was performed to estimate the likelihood of TRAGI in the two groups of transfusions after adjusting for variables found to be significant in the bivariate analysis.

Statistical analyses were conducted using SPSS, Version 21 (SPSS Inc., Chicago IL). A two-sided $p$-value less than 0.05 was considered to be statistically significant.

## Results

A total of 125 infants were included in our study; 57 (45.6%) and 68 (54.4%) in the pre and post-standardized feeding protocol respectively. There were 8 infants who died within 7 days of birth and were excluded. We did not have any infant with incomplete feeding record that had to be excluded. The mean gestational age (SD) of our cohort was 27.1 (2.9) weeks and birth weight (SD) was 915 (230) grams. Males comprised 58.4% of the cohort, 88% infants were African-American and 79.2% were born via C-section. Complete course of antenatal steroids was given to 50.4% mothers, 29.6% mothers had histological chorioamnionitis. BPD was reported in 45 (36%), PDA was treated in 35.2% infants, 27 (21.6%) with medications and 17 (13.6%) by surgical ligation and 4 infants died prior to discharge. NEC of all stages was diagnosed in 19 (15.2%) infants, of whom 17 infants were treated medically and 2 infants had surgical NEC. NEC occurred within 48 h of transfusion (TRAGI) in 6/19 (31.6%) infants, with a rate of 4.8% overall. NEC rates (15.8 vs. 14.7%) and the proportions (22.2 vs. 40%) of TRAGI in the two time periods before and after instituting the standardized feeding regimen and practice of holding

feeds during transfusion were not significantly different. Postnatal hydrocortisone was administered to 14 infants, 10 of whom did not develop NEC. Hydrocortisone was used for hypotension after surgical treatment of NEC (not associated with transfusion) in one infant. The other three infants administered postnatal hydrocortisone included two who received it during medical management of TRAGI for hypotension, one of whom was associated with a bloodstream infection. The last infant received hydrocortisone during the first week of life for hypotension and developed TRAGI 6 weeks later.

The median (range) number of transfusions prior to development of TRAGI was 1.5 [1–6]. Out of the remaining 13 infants who developed NEC but not TRAGI, 8 infants had not received any transfusion prior to onset of NEC whereas five infants received between 1 and 8 transfusions >72 h prior to development of NEC. Maternal and neonatal characteristics of three groups of infants (no NEC, NEC excluding TRAGI and TRAGI) are compared in Table 1.

On multivariable regression analysis, with gestational age, any antenatal steroids, antibiotic use for >5 days after birth and postnatal hydrocortisone as covariates, postnatal hydrocortisone (OR 8.97; 95% CI 1.17–68.46, $p = 0.034$) was associated with TRAGI. There were no significant associations with NEC.

In the second part of our study, we assessed 381 RBC transfusions during the neonatal hospitalization. Of the 381 transfusions, 189 were in the period before the feeding regimen was instituted and 192 following the regimen during which feeds were held. Table 2 shows the comparison of transfusion-related characteristics among the groups. Higher proportion (69 vs. 58%, $p = 0.014$) of transfusions in group 2 was among infants who received ventilatory support compared to the group before the feeding regimen. Transfusions were given at a lower mean postmenstrual age and weight in the latter period ($p = 0.0001$). As intended, rate of breast milk feedings increased from 45.5 to 71.9% ($p = 0.002$) of transfusions. Higher (39.1 vs. 4.2%) proportion of infants had feedings held for transfusion in the latter period, whereas 41.8 and 50% of infants were NPO more than 24 h before the transfusion in the two periods ($p = 0.0001$). TRAGI rates did not differ between the two periods whereas blood stream infection (BSI) within 24 h of transfusion tended to increase in the second epoch. Out of three episodes of transfusions with concomitant BSI in the first epoch, one associated with Enterococcus fecalis had TRAGI. During the second epoch, there were 8 transfusion episodes with concomitant BSI; one with Candida BSI was associated with TRAGI. Volume of feeds 24 h before and after transfusion was significantly higher in the group before the feeding regimen.

A binary logistic regression was performed to ascertain the effects of ventilator respiratory support, type of feeding, weight at transfusion, concomitant bloodstream infection at the time of transfusion, and whether infant was made NPO for the transfusion or was feeding through out on the likelihood of developing TRAGI. The logistic regression model showed a good fit (Hosmer and Lemeshow $p$ value = 0.99). There were no significant associations with TRAGI, including the practice of holding feeds during transfusion.

## Discussion

About 32% of NEC occurred within 48 h of a red blood transfusion and were categorized as TRAGI in our cohort. Postnatal hydrocortisone was associated with TRAGI. There was no discernible benefit to holding feeds for 12–24 h during and after transfusion on rates of TRAGI.

The rate of TRAGI varies between 20 and 74% across different studies reported in the literature [5, 9, 10, 12, 15]. Our NEC rate of 15% and TRAGI rate of 32% are broadly consistent with the literature. Postnatal hydrocortisone was associated with an increased risk of TRAGI in our study ($p$-value 0.034). Based on the timing of administration of hydrocortisone, it does not appear to be a clinically important risk factor for development of TRAGI. The risk of mortality was higher in cases with TRAGI with 83.3% infants with TRAGI surviving to discharge compared to 95.3% in no NEC group and 92.3% in NEC excluding TRAGI. Several other studies have also reported a more severe course and increased risk of mortality with TANEC/TRAGI [9, 10].

We did not find any difference in the hematocrit, volume of blood per transfusion or number of donors between groups, although several studies suggest anemia instead of pRBC transfusion to be a potential risk factor for development of NEC [8, 17, 22]. Some speculate the cause to be T-antigen activation (Thomsen-Friedenreich cryptic T antigen) on red blood cells in patients who received multiple blood transfusions from adult donors' positive for anti T-antibodies [23–25].

Our data did not show a decrease in the rate of NEC or TRAGI after implementation of a standardized feeding regimen that included withholding feeds for 12 h or more for transfusion. The benefits of standardized feeding resulting in lowering the risk of NEC have been attributed to early initiation and slow advancement of feeds [3] and we believe that we were following these practices even before the institution of standardized feeding regimen-hence making the benefits less evident. Several studies have reported the effect of withholding feeds around transfusion with conflicting results. Periaccante reported a decrease in rates of TANEC after implementing a practice of withholding feeds 4 h before until 4 h after completion of transfusion [26]. El-Dib reported a decrease in the overall

**Table 1** Maternal and neonatal characteristics

| Characteristic | No NEC (106) | NEC excluding TANEC (13) | TANEC (6) | *p*-value |
|---|---|---|---|---|
| *Maternal age* | | | | 0.41 |
| Mean (SD) | 26.7 (6.3) | 29.2 (5.7) | 26.3 (7.4) | |
| Median (IQR) | 27 (21–31) | 27 (21–42) | 24.5 (19–37) | |
| Race (% Black) | 87 | 92 | 100 | 0.95 |
| Prenatal care (%) | 95 | 100 | 100 | 0.63 |
| Rupture of membranes >18 h (%) | 13 | 23 | 17 | 0.92 |
| Prenatal Indomethacin (%) | 0.9 | 0 | 0 | 0.92 |
| Antenatal steroids (%) | 79 | 92 | 83 | 0.85 |
| Complete course ANS (%) | 51 | 54 | 33 | 0.91 |
| Chorioamnionitis (histologic) (%) | 29 | 15 | 67 | 0.21 |
| Antenatal magnesium sulfate (%) | 67 | 69 | 67 | 0.99 |
| Maternal antibiotic exposure before delivery (%) | 40 | 62 | 50 | 0.97 |
| Multiples (%) | 33 | 39 | 17 | 0.64 |
| Cesarean delivery (%) | 78 | 92 | 67 | 0.37 |
| *Gestational age (week)* | | | | 0.47 |
| Mean (SD) | 27.2 (2.9) | 27.5 (1.9) | 25.8 (3.5) | |
| Median (IQR) | 27 (25–29) | 28 (24–30) | 24.5 (23–32) | |
| *Birth weight (g)* | | | | 0.46 |
| Mean (SD) | 912 (222) | 972 (250) | 833 (335) | |
| Median (IQR) | 917 (728–1109) | 1070 (540–1250) | | |
| *1 min Apgar* | | | | 0.49 |
| Mean (SD) | 5 (2) | 5 (3) | 4 (3) | |
| Median (IQR) | 5 (3–7) | 5 (1–9) | 3.5 (0–9) | |
| *5 min Apgar* | | | | 0.53 |
| Mean (SD) | 7 (2) | 7 (1) | 6 (2) | |
| Median (IQR) | 7 (6–8) | 7 (5–9) | 6 (4–9) | |
| Male gender (%) | 57 | 62 | 83 | 0.42 |
| SGA (%) | 25 | 15 | 33 | 0.95 |
| Surfactant use (%) | 66 | 54 | 67 | 0.68 |
| Antibiotic use for >5 days after birth (%) | 42 | 46 | 67 | 0.50 |
| PDA (medical treatment) (%) | 25 | 0 | 17 | 0.26 |
| PDA ligation (%) | 12 | 23 | 17 | 0.32 |
| Vasopressor use (%) | 26 | 46 | 50 | 0.42 |
| Postnatal hydrocortisone (%) | 9 | 8 | 50 | 0.008 |
| Early onset sepsis (%) | 2 | 0 | 0 | 0.83 |
| BPD (%) | 35 | 46 | 33 | 0.38 |
| Grades 3–4 IVH (%) | 9 | 15 | 33 | 0.70 |
| Late onset sepsis (%) | 29 | 39 | 33 | 0.96 |
| ROP (%) | 12 | 8 | 33 | 0.567 |
| *Total TPN days* | | | | 0.001[a] |
| Mean (SD) | 31.4 (21.3) | 60.5 (24.7) | 49.2 (34.1) | |
| Median (IQR) | 26.5 (16–42.5) | 54 (38–124) | 37 (21–115) | |
| *Central line days* | | | | 0.003[a] |
| Mean (SD) | 33.8 (23.9) | 59.9 (25.5) | 57.2 (36.7) | |
| Median (IQR) | 27.5 (19–47.3) | 57 (36–123) | 48 (24–118) | |

**Table 1** (continued)

| Characteristic | No NEC (106) | NEC excluding TANEC (13) | TANEC (6) | *p*-value |
|---|---|---|---|---|
| *Total volume of packed RBC (ml)* | | | | 0.12 |
| Mean (SD) | 62 (50.7) | 93.8 (47.8) | 50.1 (28.9) | |
| Median (IQR) | 49.5 (26–82) | 72 (38–170) | 47 (22–87) | |
| *No. of donors* | | | | 0.968 |
| Mean (SD) | 2.63 (1.98) | 2.60 (1.52) | 2.40 (1.52) | |
| Median (IQR) | 2 (1–4) | 2 (1–5) | 2 (1–4) | |
| *Discharge weight (g)* | | | | 0.017[a] |
| Mean (SD) | 2156 (469) | 2539 (514) | 1971 (398) | |
| Median (IQR) | 2070 (1415–4270) | 2428 (1885–3452) | 2085 (1260–2345) | |
| *Discharge head circumference (cm)* | | | | 0.23 |
| Mean (SD) | 31.2 (4.3) | 32.5 (1.9) | 28.1 (7.5) | |
| Median (IQR) | 31 (30–32.5) | 32 (30.2–36.5) | 31 (17–33.5) | |
| Survived to discharge (%) | 95 | 92 | 83 | 0.026 |
| Breast milk feeds at discharge (%) | 30 | 31 | 17 | 0.690 |

*p* values based on ANOVA and chi-square test

[a]NEC excluding TANEC vs. no NEC

rates of NEC from 5.3 to 1.3% after institution of a policy of withholding feeds during transfusion [16]. De Rienzo et al. noted a decrease in NEC rates but no change in TANEC rates after withholding of feeds during transfusion [17]. Similar findings of lower rates of NEC were reported by Talavera et al after they made practice changes that included withholding of feeds during transfusion as part of quality improvement initiative across eight NICU's [27]. Doty et al. did not report any benefit of withholding feeds during transfusion on the rates of NEC [18]. In a recent systematic meta-analysis, Jasani et al. reported a benefit of withholding feeds on the incidence of TANEC [28]. In our study, transfusions in the second epoch were administered at younger ages and to infants born at earlier gestational ages. Rates of ventilator support were higher, as were rates of BSI. These risks might have been countered with an increase in breast milk use. After adjusting for these differences, we found no statistically significant associations of TRAGI with feeding practices.

The discrepancy in the results of different studies could be due to variation in study design and difference in feeding and transfusion practices. Many studies have reported lower pre-transfusion hematocrit to be a risk factor for TANEC [9, 22]. We did not find any difference in the hematocrit prior to transfusion in our two groups. The transfusion episodes have been analyzed differently in different studies. We chose to analyze each blood transfusion episode separately as we feel that there might be a change in the clinical status of infant with each transfusion and many factors like PDA, blood stream infection, feeding etc. might vary with each transfusion. Moreover, the effect of withholding or continuing feeds should not persist beyond a few hours after transfusion. Krimmel et al. demonstrated that postprandial increase in peak systolic and mean mesenteric blood flow volumes was reduced after blood transfusion. However, postprandial hyperemia was noted in response to feeds in the follow up study repeated 48–96 h after transfusion [29]. The effect of other factors like bolus vs. continuous feeds could also contribute to variations in the results. A few studies have shown an increase in splanchnic tissue oxygenation after bolus feeds but not during continuous feeds in stable preterm infants [30, 31]. In addition, we found that nearly half the infants were not feeding at the time of transfusion, consistent with some other reports [9, 10].

Withholding feeds is not without consequences; it can cause metabolic instability including changes in electrolytes and osmotic load, delay in attainment of goal feeds and may increase central line days. Our study also showed that volume of feeds was much lower 24 h post-transfusion compared to 24 h pre-transfusion in the group that had the feeding held. Given these findings and the lack of strong evidence of benefit, cautious continuation of feeds during transfusion seems reasonable.

We do acknowledge limitations of our study. It is a single center retrospective study; hence only associations can be established. The study was not powered to confirm non-inferiority of the approaches between the two time periods. However, the sample size is in line with other studies in the area and included all patients in a single moderate size level III NICU within a reasonable timespan during which other practices can be assumed to be unchanged. We did not collect

**Table 2** Blood transfusions and clinical characteristics

| Variable | Group 1 before feeding regimen $N = 189$ | Group 2 after feeding regimen $N = 192$ | $p$ value |
|---|---|---|---|
| *Resp support N (%)* | | | 0.014 |
| RA | 24 (13) | 15 (8) | |
| NC | 29 (15) | 11 (6) | |
| CPAP/NIPPV | 24 (13) | 34 (17) | |
| Vent/HFO | 112 (59) | 132 (69) | |
| *Feedings* | | | 0.0001 |
| NPO for >12 h | 8 (4) | 75 (39) | |
| Feeds continued | 102 (54) | 21 (11) | |
| NPO before | 79 (42) | 96 (50) | |
| *Type of feed N (%)* | | | 0.002 |
| BM | 46 (24) | 69 (36) | |
| Formula | 49 (26) | 23 (12) | |
| Mixed | 6 (3) | 4 (2) | |
| *PMA (weeks)* | | | 0.0001 |
| Mean (SD) | 29.6 (3.8) | 28.3 (3.4) | |
| Median (IQR) | 29 (26–33) | 28 (26–31) | |
| *Weight (g)* | | | 0.0001 |
| Mean (SD) | 1127 (522) | 956 (403) | |
| Median (IQR) | 1020 (710–1474) | 855 (650–1150) | |
| *Hct % prior to transfusion* | | | 0.491 |
| Mean (SD) | 31 (22) | 30 (13) | |
| Median (IQR) | 29.7 (26.5–31.9) | 29.1 (26.9–31.1) | |
| *PO volume 24 h before transfusion (ml)* | | | 0.001 |
| Mean (SD) | 18.4 (13.5) | 12.0 (10.4) | |
| Median (IQR) | 10 (1–22) | 4.5 (1–16.3) | |
| *PO volume 24 h after transfusion (ml)* | | | 0.0001 |
| Mean (SD) | 18.5 (13.6) | 9.4 (9.0) | |
| Median (IQR) | 0 (0–15) | 0 (0–3) | |
| *Calories/oz before transfusion* | | | 0.572 |
| Mean (SD) | 22.4 (2.1) | 22.2 (2.6) | |
| Median (IQR) | 24 (20–24) | 20 (20–24) | |
| *Calories/oz after transfusion* | | | 0.189 |
| Mean (SD) | 22.4 (2.1) | 21.7 (4.3) | |
| Median (IQR) | 24 (20–24) | 20 (20–24) | |
| *Hct % after transfusion* | | | 0.002 |
| Mean (SD) | 39.6 (4.2) | 38.2 (3.9) | |
| Median (IQR) | 39.4 (36.6–42.3) | 38.2 (35.3–40.5) | |
| *RBC volume (ml/Kg)* | | | 0.773 |
| Mean (SD) | 15.6 (2.5) | 15.5 (3.0) | |
| Median (IQR) | 15 (15–15) | 15 (15–15) | |
| TANEC *N* (%) | 2 (1) | 4 (2) | 0.685 |
| BSI within 24 h of transfusion *N* (%) | 3 (2) | 11 (6) | 0.053 |
| Hypotension within 24 h of transfusion *N* (%) | 18 (10) | 22 (11) | 0.614 |

data on the age of red cells transfused and other potential confounders like use of acid-suppression drugs, although rates are generally very low at our center. Nonetheless, in a high risk cohort of extremely preterm infants, we performed a careful investigation of transfusion-related characteristics. Our criteria for transfusion were evidence based and consistently followed as was the feeding regimen. Our results did not indicate any benefit of withholding feeds during transfusion on the rates of NEC or TRAGI.

In summary, NEC is a multifactorial disease with significant morbidity and mortality. Further randomized controlled trials to explore multiple facets of the disease are required to develop a robust preventive strategy.

**Author contributions** MB: Conceptualized and designed the study. Collected and analyzed data. Wrote the first draft of manuscript and reviewed and revised the manuscript. ML: Conceptualized and designed the study, collected data, reviewed and approved the manuscript. AH: Collected data, reviewed and approved the manuscript. GN: Conceptualized and designed the study. Analyzed data. Critically reviewed, revised and approved the manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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