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Red Blood Cell Transfusion in Premature Infants Leads to Worse Necrotizing Enterocolitis Outcomes

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Abstract

Background—Necrotizing enterocolitis (NEC) is a severe intestinal disease of premature infants with high mortality. Studies suggest a causative relationship between red blood cell (RBC) transfusion and NEC, however, whether RBC transfusion leads to worse outcomes in NEC is unknown. We sought to determine whether RBC transfusion was associated with an increased risk of surgical NEC and mortality.

Methods—In this retrospective study, 115 patients were enrolled with NEC Bell's Stage 2A or greater from 2010–2015. Patients were classified based on the timing of RBC transfusion prior to NEC: ≤72 hours, >72 hours, and no transfusion. Variables including gestational age (GA), birth weight (BW), feedings and hematocrit levels were analyzed. Outcomes were surgical intervention for NEC following RBC transfusion and mortality.

Results—23 (20%) infants developed NEC ≤ 72 hours after RBC transfusion, 16 (69.6%) required surgery with a mortality rate of 21.7% (n=5). 17 (15%) infants developed NEC > 72 hours after RBC transfusion, 12 (70.6%) required surgery with a mortality rate of 23.5% (n=4). 75 (65%) patients developed NEC without RBC transfusion, 17 (22.7%) required surgery with a mortality rate of 4% (n=3). Lower GA and BW were significantly associated with RBC

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Author Contributions

KEC and FCO contributed to data acquisition, interpretation of data, and manuscript preparation. RB contributed to data collection and patient enrollment. KPM contributed to the manuscript review. CTSI contributed with data analysis and manuscript review. MG contributed to conception and design of the study, data collection, patient enrollment, data acquisition, interpretation of data and manuscript preparation.

transfusion and the need for surgical intervention. RBC transfusion ≤72 hours prior to NEC was associated with surgical NEC (pairwise adjusted p<0.001) and mortality (pairwise adjusted p=0.048). However, multivariable logistic regression analysis revealed RBC transfusion is not an independent risk factor for surgical NEC.

Conclusions—Infants of lower GA and BW were more likely to receive an RBC transfusion prior to NEC, which was significantly associated with surgical intervention and an increasing risk of mortality. Judicious use of transfusions in premature infants may improve NEC outcomes.

Keywords

Necrotizing enterocolitis; prematurity; neonatal; anemia; surgical intervention; mortality

INTRODUCTION

Necrotizing enterocolitis (NEC) is a devastating intestinal disease occurring most commonly in very low birth weight (VLBW) premature infants with an incidence of 0.3 to 2.4 per 1000 live births in the United States. [1, 2] Despite research efforts and recent advances in neonatal medical care, morbidity and mortality rates from NEC remain unchanged. Mortality rates range from 15% to 30% and can reach 50% among patients requiring surgical intervention. [3, 4] The pathophysiology of NEC is not completely understood; however, research suggests a multifactorial etiology with no single definitive cause. Early, retrospective studies evaluating the administration of red blood cell (RBC) transfusion in neonates demonstrated an increased risk of NEC after RBC transfusion, [5–8] while more recent studies have reported no association [9, 10] or even protection from NEC after receipt of RBC transfusion. [11, 12] A recent secondary, prospective analysis performed by Patel et al. concluded that severe anemia, rather than RBC transfusion, was actually the factor associated with an increased risk of NEC. [13] Though the relationship between NEC and blood transfusion has been extensively studied, there has been no definitive evidence that blood transfusion is a causative risk factor for the development of NEC.

Neonatal transfusion standards are not consistently defined and administration of RBCs can result in complications, such as transfusion-related acute lung injury (TRALI) and immune sensitization. [6, 10, 12, 14–16] A better understanding of the relationship between RBC transfusion and the development of NEC is critical since more than 50% of VLBW infants (<1500g) receive RBC transfusions. [17] We sought to investigate the relationship between RBC transfusion and NEC at our institution, and the objective of this study was to determine if RBC transfusion in premature infants was associated with worse outcomes related to NEC.

METHODS

Study Population and Selection Criteria

This study was approved by the University of Pittsburgh Institutional Review Board Protocol number PRO09110437. We performed a 5-year secondary, retrospective analysis of a cohort of infants diagnosed with NEC from 2010 to 2015. Infants were recruited from the Magee-Womens Hospital or from Children's Hospital of Pittsburgh (CHP) of University of

Pittsburgh Medical Center (UPMC), some of whom were transferred in from outside hospitals. Criteria for enrollment into our study were defined according to modified Bell's criteria, a validated scoring system developed by Bell and colleagues in 1978, which was modified in 1987 by Kliegman et al. [18] Inclusion criteria included a modified Bell's Stage 2A NEC (pneumatosis intestinalis) or greater including peritonitis, ascites, portal venous gas, or pneumoperitoneum. [18] Infants recruited for the study were consented by a parent or legal guardian. Exclusion criteria included infants diagnosed with modified Bell's Stage 1 NEC (abdominal distention, bloody stools), congenital heart disease or other congenital anomalies, and infants whose parents declined participation or were unavailable for consent.

Data Collection

An extensive chart review was performed for each infant enrolled in the study. Patient demographics such as gestational age (GA), birth weight (BW), blood type, Apgar score at 1 and 5 minutes, and weight at the time of NEC diagnosis were collected. Clinical data including physical exam, type of feeds (breast milk vs. formula), bloody stools, hematocrit levels, radiographs, and operative reports were reviewed. In our study, the primary exposure was RBC transfusion. The primary outcome was surgical intervention specifically to address the complications of NEC following RBC transfusion and the secondary outcome was mortality. Clinical characteristics consistent with NEC were reported for infants who were either exposed to antecedent RBC transfusion or not. Temporality between RBC transfusion and clinical NEC was verified by thorough review of the medical record to accurately determine the precise sequence between exposure and outcome. Patients were classified into three cohorts: 1) RBC transfusion less than 72 hours prior to NEC diagnosis, 2) RBC transfusion greater than 72 hours prior to NEC diagnosis and 3) no RBC transfusion prior to NEC diagnosis. Patients transfused at outside facilities prior to transfer to our institution were classified similarly to inborn patients. Only RBC transfusions that occurred *before* the onset of clinical signs and symptoms consistent with NEC were evaluated. For analysis, patients were further grouped according to NEC diagnosis: 1) medical NEC, which consisted of infants who were treated non-operatively and 2) surgical NEC, which consisted of infants who underwent surgical intervention.

Transfusion Details

Indication for RBC transfusion was determined once an infant demonstrated clinically symptomatic anemia and all blood transfusions were administered based on the infant's clinical status as designated by the treating neonatologist. In this study, blood transfusion was defined as receipt of packed red blood cells. Blood prepared for all patients was washed, leukoreduced, and stored according to institutional blood bank protocols. The shelf life of transfused blood ranged from 1 to 42 days. The volume of transfused RBCs ranged from 10 to 20 milliliters per kilogram (kg) body weight of the infant.

Statistical Analysis

Categorical variables were summarized with frequencies and percentages, while continuous variables were summarized with mean ± standard deviation, or median (interquartile range) for skewed continuous variables. Variables were then assessed for association with RBC transfusion timing (no transfusion, transfusion less than 72 hours prior to diagnosis, or

greater than 72 hours prior to diagnosis) with chi-squared tests or one-way ANOVA, as appropriate. Significant overall ANOVA findings were followed up with Tukey HSD-adjusted post-hoc analysis. Other post-hoc pairwise comparisons, such as those involving categorical variables, were conducted with a Bonferroni adjustment. Subsequently, RBC transfusion timing was tested for association with the two outcomes, surgical intervention and NEC-specific death, with chi-squared tests. Multivariable logistic regression was also used to examine these outcomes while adjusting for possible confounders. Two-sided p-values < 0.05 were considered statistically significant. All analyses were conducted in IBM SPSS version 24 (IBM Corp., Armonk, NY) in conjunction with the Clinical and Translational Science Institute (CTSI) of the University of Pittsburgh.

RESULTS

One hundred and fifteen (n=115) premature infants with a diagnosis of modified NEC Bell's Stage 2A or greater were studied over a 5-year period. Patients were recruited from the neonatal intensive care units of Magee-Womens Hospital or Children's Hospital of Pittsburgh of UPMC, 20 (17.4%) of whom were transferred in from outside hospitals. The patient cohort was divided into three groups: 1) RBC transfusion less than 72 hours prior to NEC diagnosis, 2) RBC transfusion greater than 72 hours prior to NEC diagnosis, and 3) no RBC transfusion prior to NEC diagnosis. Patient demographics and clinical characteristics for each group are listed in Table 1. The gestational age ranged from 23 to 34.8 weeks, all patients meeting the definition of prematurity (<37 weeks gestation). Patient birth weight was classified as extremely low birth weight (ELBW: <1000g), very low birth weight (VLBW: 1001g – 1500g), low birth weight (LBW: 1501 – 2500g), and normal birth weight (NBW: >2500g). 23 (20%) infants developed NEC less than 72 hours following RBC transfusion, 17 (15%) infants developed NEC greater than 72 hours following RBC transfusion, and 75 (65%) infants developed NEC without receiving RBC transfusion.

Lower gestational age was significantly associated with RBC transfusion, regardless of transfusion timing ($p<0.001$). Additionally, birth weight differences across all three transfusion groups were significant ($p<0.001$). However, there was no difference between the two RBC transfusion groups with respect to gestational age (pairwise adjusted $p=0.413$) or birth weight (pairwise adjusted $p=0.627$). According to birth weight categories, 16 (42.1%) ELBW infants, 6 (16.7%) VLBW infants, and 1 (2.6%) LBW infant received an RBC transfusion less than 72 hours prior to NEC diagnosis (Table 1). This data suggests a strong correlation between low birth weight and a requirement for RBC transfusion ($p<0.001$).

Our patient cohort consisted of 75 males and 40 females. There was no significant difference among the three transfusion groups with regard to gender ($p=0.193$). Among singletons (n=107), 23 (21.5%) infants received an RBC transfusion less than 72 hours prior to NEC diagnosis and 67 (62.6%) infants did not receive an RBC transfusion prior to NEC diagnosis. By contrast, among twins (n=8), 100% of infants did not receive a transfusion prior to NEC. There was no difference in RBC transfusion rates between singletons and twins ($p=0.167$). Moreover, infants with intrauterine growth restriction (IUGR) (n=12) were more likely to receive an RBC transfusion, however, no significant difference exists between

the three transfusion groups (p=0.086). Previous studies have not examined an association between patient blood type and development of NEC; therefore, we sought to investigate for any significant differences in our cohort. We did not find a significant difference among the three transfusion groups with regard to patient blood type (p=0.688).

A significant difference in Apgar scores existed between the following groups: RBC transfusion less than 72 hours prior to NEC diagnosis group vs. no RBC transfusion prior to NEC diagnosis group (pairwise adjusted p=0.002) and RBC transfusion greater than 72 hours prior to NEC diagnosis group vs. no RBC transfusion prior to NEC diagnosis group (pairwise adjusted p=0.002). Receipt of enteral feeds did not differ significantly between the three groups. There was no significant difference in the administration of breast milk (p=0.256) or formula (p=0.853) among the three groups. The postnatal age of NEC diagnosis was significantly different among the three groups, such that infants who developed NEC at a later postnatal age received RBC transfusion at some point before their diagnosis (p<0.001). On further analysis, we discovered that this difference existed only between the following groups: RBC transfusion less than 72 hours prior to NEC diagnosis vs. no RBC transfusion prior to NEC diagnosis and RBC transfusion greater than 72 hours prior to NEC diagnosis vs. no RBC transfusion prior to NEC diagnosis (pairwise adjusted p<0.001). Patient weight at NEC diagnosis was lower in infants who required RBC transfusion regardless of the timing of transfusion when compared to infants who did not receive an RBC transfusion (p<0.001).

Hematocrit levels at the time of NEC diagnosis significantly differed among the three groups (p<0.001). However, on further analysis, we found that this difference only existed between the RBC transfusion greater than 72 hours prior to NEC diagnosis group and the no RBC transfusion prior to NEC diagnosis group (pairwise adjusted p=0.004). However, it is important to note that our data reflects hematocrit levels at the time of NEC diagnosis and some infants had been previously transfused.

Outcomes

In this study, the primary outcome was surgical intervention for a diagnosis of NEC following RBC transfusion and the secondary outcome was mortality. NEC outcomes were classified as either medical NEC or surgical NEC. Medical NEC was defined as treatment for modified Bell's Stage 2A with bowel rest and intravenous antibiotics. Surgical NEC was defined as treatment for modified Bell's Stage 2A or greater with drain placement or exploratory laparotomy. In our cohort, 45 (39%) infants required surgical intervention (Table 2). Only 1 patient underwent drain placement and ultimately required exploratory laparotomy.

40 (34.8%) infants received an RBC transfusion at some point prior to their diagnosis of NEC, including 13 outborn patients. Our cohort reveals a greater percentage of infants required surgical intervention opposed to conservative management after receiving an RBC transfusion. Our outborn patients demonstrated a similar pattern, for the majority (84.6%) of infants who received an RBC transfusion underwent surgical intervention. Thus, being outborn did not change the outcome for these patients. An analysis comparing all three transfusion groups revealed infants who received an RBC transfusion, regardless of timing,

were more likely to require surgical intervention. Further statistical analysis excluding the RBC transfusion greater than 72 hours prior to NEC diagnosis group confirmed that the results remained significant (pairwise adjusted $p<0.001$), suggesting that receiving an RBC transfusion less than 72 hours prior to NEC diagnosis is associated with surgical NEC.

12 patient deaths were recorded in our cohort (Table 3). 11 (91.7%) patients underwent surgical intervention prior to death, while 1 patient died without undergoing surgery. All but one patient death occurred within 24 to 72 hours of NEC diagnosis and were a direct result of NEC, as noted in the death summary. One death occurred 17 days after NEC diagnosis secondary to overwhelming sepsis following multiple abdominal surgeries. RBC transfusion was associated with death from NEC following surgical intervention ($p=0.007$). Further statistical analysis excluding the RBC transfusion greater than 72 hours group revealed that the results remained significant (pairwise adjusted $p=0.048$), suggesting that receiving an RBC transfusion less than 72 hours prior to NEC leads to surgical intervention and is associated with an increase in mortality. 4 (33.3%) of the deaths occurred in outborn patients; the majority (75%) of which were in the RBC transfusion less than 72 hours group, demonstrating that being outborn did not change the outcome of these patients.

To determine whether RBC transfusion is an independent risk factor for NEC, we analyzed our primary outcome (surgical NEC) and secondary outcome (mortality) against patient characteristics consistently documented to be risk factors for NEC, such as early gestational age, low birth weight, and anemia [4, 13] (Table 4). Infants who underwent surgical intervention or died had a lower gestational age compared to survivors treated conservatively with antibiotics. Gestational age was significantly different between patients in the medical NEC and surgical NEC subgroups ($p<0.001$). Furthermore, a significant difference in gestational age existed between survivors and deceased patients ($p=0.002$). Similarly, birth weights of patients in the surgical NEC group were lower compared to birth weights of the medical NEC group ($p<0.001$). Deceased patients also had lower birth weights when compared to survivors ($p=0.010$).

The severity of anemia at the time of diagnosis was significantly associated with a need for surgical intervention, but not mortality (Table 4). Hematocrit levels of infants in the surgical NEC group were lower compared to those in the medical NEC group (36.2% vs. 39.9% respectively). Additionally, deceased patients had lower hematocrit levels compared to survivors. Our results reveal that infants with lower hematocrit levels were more likely to undergo surgical intervention than infants with higher hematocrit levels ($p=0.008$). However, the severity of anemia was not significantly associated with mortality ($p=0.473$).

In order to determine if RBC transfusion was an independent risk factor for our outcomes, we used multivariable logistic regression analysis to control for key variables including gestational age, birth weight, and anemia. We found that RBC transfusion was not an independent risk factor for surgical intervention while controlling for gestational age ($p=0.328$), or birth weight ($p=0.236$). However, RBC transfusion remained an independent risk factor for both surgical intervention ($p<0.001$) and mortality ($p=0.029$) when controlling for anemia ($p<0.001$). When all three variables are simultaneously analyzed, RBC transfusion was no longer associated with either outcome ($p=0.255$).

Neither breast milk nor formula feeds were associated with surgical NEC or mortality in our patient cohort. At the time of NEC diagnosis, 37 (32.2%) infants had received formula, 34 (29.6%) infants had received breast milk, and 37 (32.2%) infants had received a combination of breast milk and formula. The type of enteral feedings for three patients prior to NEC diagnosis could not be ascertained from the medical record due to incomplete transfer records. Of note, at the time of NEC diagnosis, four infants had exclusively received parenteral nutrition. Interestingly, 11 (29.7%) formula fed infants underwent surgical intervention, compared to 16 (47.1%) breast milk-fed infants. Mortality was 10.8% (n=4) for formula fed infants and 17.6% (n=6) for breast milk-fed infants. No significant difference in surgical intervention or mortality was seen based on the type of enteral feed administered (p=0.393).

Gender did appear to play a significant role in surgical NEC, but not mortality (Table 5). 35 (46.7%) males underwent surgical intervention for NEC compared to 10 (25%) females. 8 (10.7 %) males died compared to 4 (10%) females. Our results reveal that male infants were more likely to undergo surgical intervention than female infants (p=0.023). However, gender was not associated with mortality (p=1.0).

This study demonstrates that in our cohort, there was no association between the patient's blood type and a diagnosis of NEC (Table 1). However, Thompson et al. did discover a threefold higher risk of mortality in infants who were blood type AB compared to infants of other blood types. [19] Therefore, we sought to evaluate this in our study and found no significant association between patient blood type and surgical intervention or mortality (p=0.609; data not shown), which may be related to the small numbers of infants with AB blood type in our study.

DISCUSSION

Necrotizing enterocolitis is among the most devastating complications of prematurity, particularly in infants with very low birth weights. [20] These infants are at increased risk for morbidity and mortality not only related to NEC, but to anemia, hypoxia, and intraventricular hemorrhage. Premature infants often need RBC transfusions to treat these latter clinical scenarios, but this intervention does not come without additional risk or complications. Several studies have proposed that RBC transfusion may be a risk factor for the development of NEC in premature infants. [6, 8, 21] Another study demonstrated NEC was more likely to develop in infants transfused within 24 hours of birth. [5]

The most important risk factors for NEC are low birth weight and early gestational age. [1, 4, 22, 23] Indeed, our cohort of patients was comprised of all premature infants, and all but two infants were either LBW, VLBW, or ELBW. Infants who required surgical intervention or died had lower gestational ages and birth weights compared to infants treated for medical NEC or those that survived, suggesting that early gestational age and low birth weight are risk factors for more severe outcomes after a diagnosis of NEC. Indeed, our multivariable analysis suggests that gestational age and birth weight are the driving forces for worse outcomes in our patient population.

In our analysis, we discovered that infants of lower gestational age and birth weight diagnosed with NEC were more likely to receive an RBC transfusion compared to infants of older gestational age and higher birth weight. These infants also had a significant increase in the need for surgical intervention, regardless of the timing of RBC transfusion. Although not statistically significant, Christensen et al. published higher mortality rates for infants who underwent surgery for NEC following RBC transfusion compared to infants who underwent surgery for NEC unrelated to RBC transfusion, 40% vs. 28% respectively. [8] In our cohort, infants who underwent surgical intervention were also more likely to die when compared to infants who did not undergo surgery. This may suggest that these patients have already faced irreversible injury that is unlikely to be corrected by surgical intervention. Our results reveal that hematocrit levels at the time of NEC diagnosis correlated with patient outcomes. Surgical intervention and mortality were increased in infants with lower hematocrit levels. This would suggest that anemia predisposes these infants to worse outcomes, however our multivariable analysis revealed that anemia was not the driving force for these outcomes. Indeed, several groups suggest that severe anemia in VLBW infants is a critical risk factor for NEC, however, no conclusions regarding the relationship of anemia to NEC-related outcomes were made. [13, 24, 25]

A previous study by Holman et al. found that male VLBW infants with NEC are at greater risk for death compared to females. [26] Our study suggests worse NEC-related outcomes in male infants. Males were more likely to undergo surgical intervention for NEC compared to females, however, there was no difference noted in mortality.

Although our results suggest a correlation between RBC transfusion and mortality, there are limitations to our study. First, this is a retrospective, secondary analysis of a cohort of premature infants with NEC. Data acquisition is dependent on the accuracy and completeness of the database and medical records. Furthermore, some of our infants were transferred in from non-UPMC affiliated hospitals, further affecting the precision of data acquisition. However, we observed similar trends among our inborn and outborn patients with regard to surgical intervention and mortality following RBC transfusion. Second, our cohort consisted of 115 patients, a small sample size, which limited our ability to adjust for multiple confounders and may make it difficult to see significant associations. Third, the precise age of transfused blood is unknown; thus, we were unable to determine if a correlation between the age of blood transfused and outcome exists. A recent study by Heddle et al. found no significant difference in mortality secondary to the duration of blood storage in patients who underwent transfusion. [27] Fourth, diet status at the time of RBC transfusion was not consistent among the cohort. Nutrition in premature infants is important for health and development, such that the type of feeds (breast milk vs. formula), as well as timing of feeds, have been extensively studied in the setting of NEC. [28–31] Importantly, Gephart et al. found that *nil per os* (NPO) status during RBC transfusion was found to be protective against the development of NEC. [32] Given this study, several neonatologists at our institution changed their practice to keep infants NPO during RBC transfusion, however, this practice was not uniform throughout the study period. Additional literature has emerged regarding diet status during transfusion, but there is no consensus on the timing of reintroduction of enteral feeds. [6, 33] Finally, the surgical indications for NEC can be quite variable with patients exhibiting varying clinical presentations, thus introducing the

possibility of bias in our analysis. In general, the only absolute indication for surgical intervention is intestinal perforation and the relative indications are failure of medical management, portal venous gas, abdominal wall erythema, palpable abdominal mass, and a fixed bowel loop on a radiograph. [34–36] It is worth highlighting that most intestinal perforations are evidenced by pneumoperitoneum on a radiograph, a finding that is specific, but not necessarily sensitive for NEC. In addition, the listed relative indications can be quite subjective, committing some, but not all, patients to surgical intervention. Surgery was performed on our cohort according to the attending pediatric surgeon's clinical judgment in regards to the absolute and relative indications for each patient.

CONCLUSIONS

Consistent with other groups, our cohort illustrates that NEC primarily affects infants of early gestational age and low birth weight. As infant gestational age and birth weight decreased across the cohort, we observed a correlation between earlier gestational age and lower birth weight and receipt of RBC transfusion. These infants who received an RBC transfusion, regardless of timing, had a significant increase in the need for surgical intervention for NEC. Understandably, surgery increases the risk of mortality and indeed, the infants in our study who underwent surgical intervention for NEC were more likely to die. Although our analysis does not indicate a correlation between RBC transfusion and NEC diagnosis, we reveal that in the setting of NEC, RBC transfusion is associated with an increased risk of surgical intervention and ultimately, mortality in infants of lower gestational ages and birth weights. Given our results, we suggest judicious use of RBC transfusion in premature LBW infants to not only avoid transfusion-related complications, but also decrease the risk of NEC-related complications in these infants. Further investigation with randomized controlled trials is needed to clarify if causality exists between RBC transfusion and the development of NEC.

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Glossary

NEC	Necrotizing enterocolitis
VLBW	Very low birth weight
RBC	Red blood cell
TRALI	Transfusion-related acute lung injury

CHP	Children's Hospital of Pittsburgh
UPMC	University of Pittsburgh Medical Center
GA	Gestational age
BW	Birth weight
CTSI	Clinical and Translational Science Institute
ELBW	Extremely low birth weight
LBW	Low birth weight
NBW	Normal birth weight
IUGR	Intrauterine growth restriction
NPO	*nil per os*

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Table 1

Patient Demographics and Clinical Characteristics.

	RBC Transfusion ≤ 72 hrs. prior to NEC diagnosis (n = 23)	RBC Transfusion > 72 hrs. prior to NEC diagnosis (n = 17)	No RBC transfusion prior to NEC diagnosis (n = 75)	P value
Gestational Age (weeks)	27.01 ± 0.5; 23–34	26.10 ± 0.4; 24–30	31.19 ± 0.3; 26–34.86	**<0.001**
Birth Weight (g)	901.61 ± 62.6; 470–1502	774.41 ± 56.1; 350–1320	1580.01 ± 56.8; 664–3060	**<0.001**
ELBW (n = 38)	16	14	8	
VLBW (n = 36)	6	3	27	**<0.001**
LBW (n = 39)	1	0	38	
NBW (n = 2)	0	0	2	
Gender				
Male (n=75)	69.6% (16/23)	82.4% (14/17)	60% (45/75)	0.193
Female (n=40)	30.4% (7/23)	17.6% (3/17)	40% (30/75)	
Twin Gestation	0	0	8	0.167
Blood type				
A	9	4	22	0.688
B	8	6	13	
AB	1	0	1	
O	5	9	33	
Presence of IUGR	21.7% (5/23)	11.8% (2/17)	6.7% (5/75)	0.086
Apgar score (5 min)	7; 2–9	6; 2–9	8; 3–9	**0.002**
Enteral feeds	100% (23/23)	94% (16/17)	96% (72/75)	
Breast Milk	71.4% (15/21) *	76.4% (13/17)	58.1% (43/74) #	0.256
Formula	61.9% (13/21) *	70.6% (12/17)	66.2% (49/74) #	0.853
Postnatal Age (days) at NEC diagnosis	23.13; 7–38	22.35; 7–64	11.23; 3–39	**<0.001**
Weight (g) at NEC diagnosis	1119.3; 590–2151	987.8; 400–2100	1618; 677–2650	**<0.001**
HCT level (vol. %) at NEC diagnosis	36.8; 26.2–51.9	33.9; 22–44.7	40; 24.9–55.1	**<0.001**

Data reported as mean ± standard error of the mean; range (number of patients).

RBC, red blood cell; NEC, necrotizing enterocolitis; ELBW, extremely low birth weight; VLBW, very low birth weight; LBW, low birth weight; NBW, normal birth weight; IUGR, Intrauterine growth restriction; N/A Not applicable; HCT, hematocrit

* 2 patients with unknown type of enteral feeds

1 patient with unknown type of enteral feeds

Table 2

Clinical Management of NEC.

	RBC Transfusion ≤ 72 hrs. prior to NEC diagnosis (n = 23)	RBC Transfusion > 72 hrs. prior to NEC diagnosis (n = 17)	No RBC transfusion prior to NEC diagnosis (n = 75)	P value
Medical NEC (n = 70)	7 (30.4%)	5 (29.4%)	58 (77.3%)	**<0.001**
Surgical NEC (n = 45)	16 (69.6%)	12 (70.6%)	17 (22.7%)	**<0.001**

Data reported as number of observations (percent within group).

RBC, red blood cell; NEC, necrotizing enterocolitis

Table 3

Mortality.

	RBC Transfusion ≤ 72 hrs. prior to NEC diagnosis (n = 23)	RBC Transfusion > 72 hrs. prior to NEC diagnosis (n = 17)	No RBC transfusion prior to NEC diagnosis (n = 75)	P value
Death, Surgery (n = 11)	4 (17.4%)	4 (23.5%)	3 (4%)	**0.007**
Death, No Surgery (n = 1)	1 (4.3%)	0 (0)	0 (0)	

Data reported as number of observations (percent within group).

RBC, red blood cell; NEC, necrotizing enterocolitis

Table 4

Distribution of patient characteristics based on NEC outcomes.

	Medical NEC	Surgical NEC	P value	Alive	Deceased	P value
GA (weeks)	30.88 ± 0.33; 24.57–34.86	27.6 ± 0.39; 23–33.29	**<0.001**	29.92 ± 0.30; 23.71–34.86	26.99 ± 0.85; 23–32.29	**0.002**
BW (grams)	1540 ± 64.89; 664–3060	991.18 ± 56.55; 350–1900	**<0.001**	1370.04 ± 54.64; 350–3060	940.75 ± 109.18; 470–1752	**0.01**
HCT levels	39.9 ± 0.9; 24.9–55.1	36.2 ± 0.8; 22–51.9	**0.008**	37.0 ± 0.7; 29–43	38.6 ± 1.4; 22–55.1	0.473

Data reported as mean ± standard error of the mean; range.

NEC, necrotizing enterocolitis; GA, gestational age; BW, birth weight; HCT, hematocrit

Table 5

Distribution of patient outcomes based on gender.

	Male (n = 75)	Female (n = 40)	P value
Surgical NEC (n = 45)	35 (46.7%)	10 (25%)	**0.023**
Deceased (n = 12)	8 (10.7%)	4 (10%)	1.0

Data reported as number of observations (percent within group).

NEC, necrotizing enterocolitis