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Associations Between Red Blood Cell Transfusions and Necrotizing Enterocolitis in Very Low Birth Weight Infants

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Abstract:

Background: Necrotising enterocolitis (NEC) is a serious inflammation of the bowel which mostly affects preterm infants. Two to five percent of all admissions to the Neonatal Intensive Care Unit (NICU) are because of NEC. In 85% cases, NEC affects very low birth weight (VLBW) infants (<1500 g) and is a leading cause of mortality and morbidity in preterm neonates. This study aimed to analyze the association between NEC & red blood cell transfusion in very low birth weight in the Neonatal intensive care of Benha University Hospital &Benha Children Hospital. **Methods:** This was a retrospective case-control study that was conducted on Very Low Birth Weight Infants in Neonatal Intensive Care Units of Benha University Hospital and Benha Children Hospital from November 2018 to November 2020 to identify all infants diagnosed with second stage of NEC or more according to modified Bell's criteria who were hospitalized to Benha University Hospital& Benha Children Hospital. The number of transfused patients, the frequency of transfusions per patient and the amount of transfused PRBC (ml) were compared in NEC and control groups. **Results:** The results showed that the frequency of blood transfusion during NICU admission was significantly higher in the NEC group compared to the control group, with a mean of 3.32 ± 0.84 in cases and 1.40 ± 0.55 in controls (P<0.001). regarding logistic regression analysis revealed that the frequency of blood transfusion during NICU admission was significant predictors for NEC patients (P<0.001). In our study, the volume of blood for each transfusion was significantly lower in NEC group compared to controls, with a mean of 17.69 ± 1.37 ml/kg in cases and 19.29 ± 1.23 ml/kg in controls (P<0.001). The total volume of red blood cells (RBC) transfused was also significantly higher in NEC group compared to controls, with a mean of 58.73 ± 15.43 ml/kg in cases and 26.78 ± 10.35 ml/kg in controls (P<0.001). regarding univariate logistic regression analysis revealed that volume of blood for each transfusion in ml/kg, Total volume of RBC in ml/kg was significant predictors for NEC cases (P<0.001), while in Multivariate logistic regression analysis none of these factors was significant predictors for it. Regarding outcome of studied groups, in NEC groups the survivors were 21 (44.7 %), non survivors were 26 (55.3%) while in control group the Survivors were 70 (72.9%) & non survivors were 21 cases (27.1%). **Conclusion:** Our study revealed that transfusion of red blood cells was significantly associated with the development of NEC in very low birth weight infants. The frequency of blood transfusion during NICU admission was significantly higher in the NEC group compared to the control group, and the total volume of RBC transfusion was also significantly higher in NEC group compared to controls.

Key words: Red Blood Cell Transfusions, Necrotizing Enterocolitis, Very Low Birth Weight Infants

Introduction

Necrotizing enterocolitis (NEC) is a serious inflammation of the bowel which mostly affects preterm infants. Two to five percent of all admissions to the Neonatal Intensive Care Unit (NICU) are because of NEC [(1)].

In 85% cases, NEC affects very low birth weight (VLBW) infants (<1500 g) and is a leading cause of mortality and morbidity in preterm neonates. The mortality rate of NEC in general is around 30%, while extremely low birth weight infants (<1000 g) and those who need surgery, have a mortality rate of 40 to 45 % [(2)].

Prematurity is the most important risk factor for NEC because of immature bowel protective barriers and local host defenses, such as secretory immunoglobulin A (IgA), mucosal enzymes, and immature bowel motility [(3)].

The pathologic features of NEC are inflammation beginning in the mucosa and often extending through the bowel wall and associated with ischemic necrosis. The distal ileum and proximal colon are most commonly affected [(4)].

In addition, preterm neonates are more likely to have an abnormal pattern of intestinal colonization (dysbiosis) early at birth, which is perfect for pathogenic bacteria to consolidate and NEC to develop [(5)].

There are many other risk factors of NEC described in the literature, such as early enteral feedings, absent/reverse end-diastolic umbilical artery Doppler flow, patent ductus arteriosus (PDA) and its treatment with indomethacin or ibuprofen, etc. Hypoxic–ischemic events, such as low Apgar scores, umbilical artery catheterization, episodes of apnea or bradycardia, do not play the main role in the pathogenesis of NEC but may be important additional factors [(6)].

Probably the most controversial risk factor for NEC is red blood cell transfusions (RBCT). The association between NEC and RBCT has been shown in several studies [(7)].

But in those studies, infants who were suspected to have a transfusion associated NEC were more likely to be premature, had lower birth weight or had higher unadjusted mortality rate. Because of that, many discussions arose, and some of the published studies questioned this association [(8)].

This study aimed to analyze the association between NEC & red blood cell transfusion in very low birth weight in the Neonatal intensive care of Benha University Hospital & Benha Children Hospital.

Patients and Methods

This was a retrospective case-control study was conducted on Very Low Birth Weight Infants in Neonatal intensive care units of Benha University Hospital & Benha children hospital from (November 2018 to November 2020) to identify all infants diagnosed with second stage of NEC or more according to modified Bell ‘s criteria who were hospitalized to Benha University Hospital & Benha Children Hospital. The number of transfused patients, the frequency of transfusions per patient and the amount of transfused PRBC (ml) were compared in NEC and control groups.

It comprised very low birth weight infants of both sexes after obtaining an informed consent from caregiver.

The study was under the following Inclusion and exclusion criteria: -

Inclusion criteria:

- Very low birth weight infants (<1500 g).

- Both sexes (Males and females).
- Infants with second stage of NEC according to modified Bell**'s** criteria as abdominal distension, increased gastric residuals (More than 20% of enteral feeding volume), or blood in the stools (macroscopically or microscopically) [9].

Bell's stages [10]:

Bell's stage1 (suspected disease):

- Mild systemic disease (apnea, lethargy. slowed heart rate, temperature instability)
- Mild intestinal signs (abdominal distention, increased gastric residuals, bloody stools)
- Non-specific or normal radiological signs

Bell's stage 2 (definite disease):

- Mild to moderate systemic signs.
- Additional intestinal signs (absent bowel sounds, abdominal tenderness).
- Specific radiologic signs (pneumatosis intestinalis or portal venous gas.
- Laboratory changes (metabolic acidosis, too few platelets in the blood stream).

Bell's stage 3 (advanced disease):

- Severe systemic illness (low blood pressure).
- Additional intestinal signs (striking abdominal distention, peritonitis).
- Severe radiologic signs (pneumoperitoneum).
- Additional laboratory changes (metabolic and respiratory acidosis, disseminated intravascular coagulation)
- Conformation of the NEC diagnosis by clinical examinations & abdominal imaging including two views abdominal radiography, and ultrasonography, performed as soon as NEC was suspected and serial follow-up with both.

Exclusion criteria:

- Any congenital malformation.
- Full term infants.

Ethical consideration:

Approval of the study protocol by an Ethical Scientific Committee of Benha University was obtained and informed consent was obtained from the parents before enrollment in the study (MS-24-7-2021).

Methods:

The infants were defined as the NEC case group &Our control group was selected by matching each NEC group patient with an infant who had a similar gestational age and birth weight and had no diagnosis or even suspicion of NEC.

Transfused PRBC (ml) was compared in NEC and control groups.

The number of transfused patients, the frequency of transfusions per patient and the amount of transfused PRBC (ml) were compared in NEC and control groups.

-A standardized data sheet was utilized to record perinatal history, clinical examination and investigations that are performed, as follows:

Full history taking:

- Personal history of mother: gestational age, sex, residence and socio-economic Status.
- Present history: abdominal distension, increased gastric residuals (More than 20% of eternal feeding volume), or blood in the stools (macroscopically or microscopically).
- Prenatal history.

-Any maternal risk factor during pregnancy e.g., chronic medical illness-infection-drug abuse–polyhydraminous–premature rupture of membrane- trauma.

-Fetal risk factors e.g., multiple gestation–fetal distress erythroblastosis fetalis.

- Past history: History of similar condition, a preterm first birth is the best predictor of a preterm second births other diseases e.g., Hypertensive disorders infection and operations.

- Onset: Onset is typically in the first four weeks of life.
- Outcome & treatment: number of survivors &non survivors of study groups and line of treatment if medically or surgically treated.
- Long-term complications of medical NEC include bowel obstruction and anemia.
- Family history: History of prematurity.

Clinical examination:

- General examination: Vital sign, anthropometric measurements (Weight and height), exclude congenital anomalies.
- Chest examination: Decrease air entry.
- Heart examination: Murmur and exclude heart anomalies, PDA.
- Abdominal examination: distention, absent bowel sounds, abdominal tenderness, erythema of the abdominal wall).

Study investigation:

Laboratory investigation:

- Complete blood count (CBC) was done for all samples using sysmex KX-21N (Sysmex Corporation, New York, USA) for red blood cell (RBC) count, hemoglobin level, hematocrit value, WBC count (total and differential), and platelet count.
- C-reactive protein: Quantitative measurement of the level of C- reactive protein (CRP). Estimation was carried out using the test kit (Cromatest) at 0h of clinical presentation. The AVITEX- CRP latex particles are coated with antibodies to human CRP. When the latex suspension is mixed with serum containing elevated CRP levels on a slide, clear agglutination was seen within 2 minutes. Specimen collection and storage: Fresh sample of venous blood was allowed to clot form and retract centrifuge clotted blood sample and collect serum, store at 2-8 oC AVITEX-CRP had a detection limit of 6 mg/L of CRP in the patient's serum.
- Serum electrolytes (Na^+ and K^+).
- Arterial Blood GAS.
- Chest X-ray: With evidence of respiratory distress.
- Abdominal X-ray &Ultrasound.

Plain abdominal radiographs were performed according to the following protocol at the bedside, anteroposterior view, patient in supine position, vertical X-ray beam, and cross table view with a portable X-ray system multi mobile 2.5 Siemens and Fuji film dry computed radiography systems, exposition data we used 45-50 kV, 4-5 mAs.

AUS examinations were carried out at the bedside, by a radiologist and trained neonatologist together, both were aware of clinical staging, baby's condition, X-ray, and ultrasound were looked into twice before giving radiological or AUS report (because we wanted to compare the clinical condition, X-ray, and ultrasound findings), with mobile ultrasound units and high-frequency linear ultrasound transducers (Philips HD 11, 3-12 MHz probe; Son site M-turbo, and 6-13 MHz probe).

- Echocardiography: If PDA is suspected
- Cranial ultrasonography: To rule out any congenital anomalies.

Statistical analysis:

The collected data were tabulated and analyzed using SPSS version 24 software (SpssInc, Chicago, ILL Company). Categorical data were presented as numbers and percentages. Chi square test (X^2), were used to analyze categorical variables. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was

used to analyze normally distributed variables among 2 independent groups. Spearman's correlation coefficient (rho) was used to assess correlation between nonparametric variables. Regression analysis was used to investigate the risk of association. ROC curve was used to detect cutoff values with optimum sensitivity and specificity. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

Results:

Table (1) shows that the mean gestational age in cases was 30.15±0.93 weeks, and consisted of 26 males(55.3%) &21 females(44.7%) ,31.9% of cases were delivered vaginally while 68.1% was born by c.s , the mean of maternal age was 28.74±3.61 year and the mean weight was 1180.11±91.08 (gm) while in control group the mean gestational age was 30.84±0.97 weeks, consisted of 52 males (54.2%)& 44 females(44.8%) , the mean of maternal age was 26.30±3.93 year , the mean weight was 1274.48±83.58 (gm)and 33.3% of control group were delivered vaginally while 66.7% was born by c.s. the NEC group has statistically higher incidence of length of hospital than control group.

Table (2) shows that NEC group has statistically higher level of WBCs, CRP, positive blood culture & metabolic acidosis than control group while was lower level in HG&HCT than control group, in NEC group occult blood in stool was 47 (100%).

Table (1): Comparison of the studdied groups regarding sociodemographic data.

Characteristics		Cases (n=47) (mean ± SD)		Control group (n=96) (mean ± SD)		Test of sig.	p-value
Gestational Age(weeks)		30.15 ±0.93		30.84 ±0.97		0.7	0.2
Weight(gm)		1180.11 ±91.08		1274.48 ±83.58		4.1	<0.001*
Maternal age(y)		28.74 ±3.61		26.30 ±3.93		3.7	<0.001*
		No	%	No	%		
Sex	Female	21	44.7%	44	45.8%	0.02	0.9
	Male	26	55.3%	52	54.2%		
Mode of delivery	CS	32	68.1%	64	66.7%	0.03	0.9
	NVD	15	31.9%	32	33.3%		
Length Of hospital stay(d) (mean ± SD)		20.79±4.80		17.24±5.60		3.7	<0.001*

*: significant, SD: standard deviation, cs: cesarean section, NVD: normal vaginal delivery.

Table (2): Comparison of the studied groups regarding lab. results

Characteristics	Cases (n=47) Mean ±SD		Control group (n=96) Mean ±SD		t	p-value
HB(g/dl)	8.81±0.41		9.26±0.67		4.9	<0.001*
HCT %	28.87±1.98		30.43±2.42		3.8	<0.001*
WBCs($x10^3$)	14.54±3.73		10.57±5.47		5.1	<0.001*
Platelets ($x10^3$)	154.68±66.42		224.04±98.80		4.9	<0.001*
Na (mmol/l)	129.98±3.14		128.68±3.33		2.2	0.01*
K (mmol/l)	4.86±0.34		4.32±0.51		7.5	<0.001*
CRP (mg/l)	93.79±54.48		66.81±50.28		2.9	0.002*
	No.	%	No.	%	X^2	p-value
Positive Blood culture	33	70.2%	32	33.3%	17.3	<0.001*
Metabolic acidosis	31	66.0%	38	39.6%	8.8	0.003*
Occult blood in stool	47	100.0%	0	0.0%	---	---

WBCs: white blood cells, CRP:C-reactive protein *: significant, SD: standard deviation ,t :Student t-test , X^2 :Chi square test .

Table (3) shows that the NEC cases has statistically higher regarding frequency of blood transfusion in NICU, volume of blood transfusion for each transfusion &total volume of RBCS than control groups.

Table (4) shows that there was statistically significant difference between studied groups regarding outcome as non survivors were higher in NEC groups than control groups.

Table (5) shows stages of Bells in NEC group, stage II is higher than stage III. Number of stages II was 29 cases (61.7%) while stage III was 18 cases (38.3%).

Table (6) shows that univariate logistic regression analysis reveals that frequency of blood transfusion in NICU, volume of blood transfusion for each feed in ml/kg, Total volume of RBC in ml/kg was significant predictors for NEC cases, while in Multivariate logistic regression analysis none of these factors was significant predictors for it.

Table (3): Comparison of the studied groups regarding blood transfusion.

Characteristics	Cases (n=47) Mean ± SD	Control group (n=96) Mean ± SD	t	p-value
Frequency of blood transfusion in NICU(No)	3.32±0.84	1.40±0.55	14.3	<0.001*
Volume of blood for each transfusion (ml/kg)	19.29±1.23	17.69±1.37	7.1	<0.001*
Total volume of RBC (ml/kg)	58.73±15.43	26.78±10.35	12.9	<0.001*

*: significant, t: Student t-test, SD: standard deviation.

Table (4): Comparison of the studied groups regarding outcome.

Characteristics		Cases (n=47)		Control group (n=96)		X^2	p-value
		No	%	No	%		
Outcome	non survivors	26	55.3%	26	27.1%	10.9	<0.001*
	survivors	21	44.7%	70	72.9%		

X^2 :Chi square test *: significant .

Table (5): NEC cases regarding Bells stages.

Characteristics	Cases (n=47) No.	%
Stage II	29	61.7
Stage III	18	38.3

Table (6): Univariate and Multivariate logistic regression analyses of various variables for prediction of NEC regarding blood transfusion.

	Univariate analysis				Multivariate analysis			
	p-value	OR	95%CI		p-value	OR	95%CI	
frequency of blood transfusion in NICU(N)	<0.001*	290.864	80.772	1010.675	0.43	2.88	0.02	29.01
volume of blood for each transfusion(ml/kg)	<0.001*	0.399	0.283	0.562	0.97	1.06	0.06	17.48
total volume of RBC in(ml/kg)	<0.001*	10.177	10.112	10.245	0.59	0.69	0.18	2.61

Discussion

In our study, among neonates with NEC there were 26 males (55.3 %) and 21females (44.7%). While in control group there were 52 males (54.2%) &44 females (45.8%) (P=0.9).

This result comes in accordance with the previous study [11] where it was reported that (58.8%) were males and (41.2%) were females with male to female ratio 1.42:1with male predominance.

Our study revealed that, the level of Hb was significantly lower in the NEC group compared to the control group, with a mean of (8.81 ± 0.41 g/dl) in cases and 9.26 ± 0.67 g/dl in controls (P<0.001).

This is in agreement with others [12], who found that 22% of neonates who developed NEC had anemia.

This was also in accordance with the study which reported that anemia of multifactorial origin is observed in patients with NEC [13].

Iatrogenic anemia may contribute to the problem, since frequent blood sampling is mandatory. In ill infants less than 1000 g whose blood volumes are less than 80 ml, phlebotomy losses may exceed 10% of the blood volume each day [13].

The results showed that the frequency of blood transfusion during NICU admission was significantly higher in the NEC group compared to the control group, with a mean of 3.32 ± 0.84 in cases and 1.40 ± 0.55 in controls (P<0.001). regarding logistic regression analysis revealed that the frequency of blood transfusion during NICU admission was significant predictors for NEC patients (P<0.001).

In agreement to our results, transfusion practices in VLBW infants in six NICUS and in multivariate analysis was compared, 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) [7]. Since then, sporadic cases of "transfusion-associated" NEC continued to be recognized by clinicians, as exemplified by the case reports by some researchers [14,15].

In our study, the volume of blood for each transfusion was significantly lower in NEC group compared to controls, with a mean of 17.69 ± 1.37 ml/kg in cases and 19.29 ± 1.23 ml/kg in controls (P<0.001). The total volume of red blood cells (RBC) transfused was also significantly higher in NEC group compared to controls, with a mean of 58.73 ± 15.43 ml/kg in cases and 26.78 ± 10.35 ml/kg in controls (P<0.001). regarding univariate logistic regression analysis revealed that volume of blood for each transfusion in ml/kg, Total volume of RBC in ml/kg was significant predictors for NEC cases (P<0.001), while in Multivariate logistic regression analysis

none of these factors was significant predictors for it.

This is in agreement with other researchers [16] who showed that infants whose received larger mean volumes of total blood developed NEC with mean (27.75±8.77 ml/kg) than non-NEC infants with (15.25±0.5 ml/kg).

This is in agreement with the results of this present study is that study which revealed that the volume of PRBC transfusion was higher in NEC infants than another group (adjusted OR 1.04, 95% CI 1.0, 1.1, p = 0.043). more infants in the NEC group (47 vs. 27, p < 0.001) required more transfusions (three vs. 0.5, p < 0.001) during hospital course [8].

This is disagreement with the study done in 2018 [17] which revealed no evidence of an association between PRBC transfusion &NEC in matched case-control studies (OR: 0.51; 95% cl:0.34-0.75; P =<0.01).

Moreover, in a prospective multicenter study of 600 infants, it was found that severe anemia and not PRBC transfusion increased the risk of NEC [18].

A number of clinical studies suggest an association between RBC transfusions and NEC, although these findings have not been consistently proven in meta-analyses [18,19].

Another study that combined seven case-control studies (480 blood transfusion cases, 2,845 control cases) showed similar results in a random-effects model (OR = 3.35, 95% CI: (1.54–7.27)) [20].

It was found that the risk of NEC was significantly higher in infants who received a blood transfusion compared to those who did not, and that the risk increased with the volume of blood transfused [21].

Regarding outcome of studied groups, in NEC groups the survivors were 21 (44.7 %), non survivors were 26 (55.3%) while in control group the Survivors were 70 (72.9%) & non survivors were 21 cases (27.1%).

This in agreement with others [8] who reported significantly, more infants died in the NEC group (20 vs. three, (p < 0.003).

Moreover, it was reported that, the mortality rate in NEC ranged from 15–40% [4]

NEC is associated with high mortality – 20–60% according to various sources, thus early diagnosis is crucial [22].

Conclusion:

Our study found that transfusion of red blood cells was significantly associated with the development of NEC in very low birth weight infants. The frequency of blood transfusion during NICU admission was significantly higher in the NEC group compared to the control group, and the total volume of RBC transfused was also significantly higher in NEC group compared to controls.

Conflict of interest

None of the contributors declared any conflict of interest.

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