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Original Article

Risk Factors for Necrotizing Enterocolitis in Newborns Admitted to Neonatal Intensive Care Unit

Zain Knaj[1], Adnan Dayoub[2]

[1] *Department of Pediatric, Tishreen University, Faculty of Medicine, Lattakia, Syria.*
[2] *Department of Pediatric, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.*

[1]*Corresponding Author : zainkknn@gmail.com*

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Abstract *- Background: Necrotizing enterocolitis (NEC) remains a common complication in neonates admitted to the neonatal intensive care unit (NICU) with poor outcomes due to its threatening gastrointestinal and neurodevelopmental complications, especially in premature neonates. Objective: This study aims to evaluate maternal and neonatal risk factors associated with the occurrence of NEC in neonates. Materials and Methods: The research applies an analytic prospective cohort study for the period of one year (2022 – 2023) at Tishreen University Hospital in Lattakia, Syria. The current study compares between two groups of neonates according to gestational age: group I consists of 25 neonates with a diagnosis of NEC, whereas Group II consists of 361 neonates without NEC. Results: The results show that 6.5% of the study population had NEC, which was observed more frequently in premature neonates than in full-term neonates (4.4% versus 2.1%). In full-term neonates, the need for respiratory support (RR 4.2), presence of congenital heart anomalies (RR 2.4), gestational hypertension (RR 3.4), transfusion of blood (RR 5.5), presence of anemia (RR 7.7) and SGA (RR 4.02) were independent factors that associated with the risk of progression NEC. In premature neonates, the need for respiratory support (RR 2.1), presence of congenital heart anomalies (RR 3.2), transfusion of blood (RR 9.5), presence of anemia (RR 7.3), and use of the formula for feeding (RR 5.4) were independent factors that associated with the risk of progression NEC. Conclusion: There is a significant prevalence of NEC in our health center, and the presence of anemia and blood transfusion represented the most important warning flags that may predispose to NEC in both full-term and premature neonates, in addition to the presence of other risk factors.*

Keywords *- Full term, Necrotizing enterocolitis, Neonates, Premature, Risk factors*.

1. Introduction

Necrotizing enterocolitis (NEC) is defined as a disorder manifested by ischemic necrosis of the intestinal mucosa [1,2,3]. It represented the most common gastrointestinal emergency in the neonatal period, with an incidence ranging from 0.7 to 1 per 1000 live births in the USA [4]. Incidence is related inversely to birth weight and gestational age, in which 90% of cases occur in very low birth weight infants (<1500 g) born at <32 weeks gestation [5,6,7]. Pathogenesis of NEC remains unclear, which varies according to gestational age [8]. In preterm infants, NEC is a multiple-factorial disease that requires the concurrent presence of an immature intestinal tract and immune system, triggers that lead to dysbiosis, and an exaggerated inflammatory host response with the release of cytokines [9,10,11]. NEC in term neonates is frequently associated with underlying conditions such as congenital heart disease, polycythemia, and sepsis that lead to impaired mesenteric oxygenation and result from poor perfusion along with non-human milk feeding [12,13]. Sudden change in feeding tolerance is represented as the most frequent clinical sign of NEC [14]. In addition, there are many abdominal signs and nonspecific systemic findings such as apnea, respiratory failure, lethargy, temperature instability, and hypotension in severe cases [15]. The definite diagnosis of NEC is made from either surgical or postmortem intestinal specimens that revealed histological findings of inflammation, infarction, and necrosis [16,17,18]. The modified Bell staging criteria represent a uniform clinical definition of NEC depending on the severity of systemic, intestinal, radiographic, and laboratory findings. Neonates are classified into three stages, and III represents an advanced stage of NEC [19]. NEC is associated with substantial medical burdens to both families and society. Therefore, it is essential to identify risk factors for NEC in neonates and develop effective prevention strategies, which are considered more important than expansion in advanced diagnostic strategies and treatment to improve outcomes. Therefore, this study aimed to investigate the risk factors for NEC in infants admitted to neonatal ICU.

2. Patients and Methods

2.1. Study Population

After approval by the local research ethics committee, an analytic-prospective cohort Study was conducted on neonates admitted at the neonate intensive care unit (NICU) of Tishreen University Hospital over a period of one year (April 2022 -2023).

2.1.1. Inclusion Criteria were as Follows

Neonates of both sexes, all gestational ages, and birth weight who developed NEC stage ≥ 2 according to modified Bell's staging criteria.

2.1.2. Exclusion Criteria

Neonates with the presence of one of the following: genetic metabolic disorders, significant congenital gastrointestinal anomalies, neonates who underwent abdominal surgical interventions before the occurrence of NEC.

A complete history, review of systems, physical examination including measurements of weight, length, and head circumference, and laboratory investigations including complete blood count, C-reactive protein (CRP), blood glucose, electrolytes, and blood culture were performed. An abdominal radiograph was performed for all neonates, and an echocardiogram was performed where there was doubt about the presence of cardiac defects.

Patients were assigned according to gestational age to premature neonates (group I included patients with NEC 17 cases, and group II included patients without NEC 134 cases) and full-term neonates (group III included patients with NEC 8 cases, and group IV included patients without NEC 227 cases). Characteristics of the study population were compared according to the presence of NEC and gestational age.

2.2. Statistical Analysis

IBM SPSS version 20 was used to perform the statistical analysis. Basic Descriptive statistics included means, standard deviations (SD), median, Frequency, and percentages. To examine the relationships and comparisons between the two groups, the chi-square test or Fisher's test was used. Independent t-student t-tests were used to compare 2 independent groups.

Multivariate logistic regression analysis was performed to estimate independent risk factors. This model included risk factors first identified through univariate analysis. All the tests were considered significant at a 5% type I error rate($p<0.05$), β:20%, and power of the study:80%.

3. Results

The study included a group of 386 neonates who fulfilled the study criteria. Gestational age ranged from 27 to 40.3 weeks, with a mean age of 36.08±2.7 weeks. Birth weight ranged from 740 to 4550 g, with a mean weight of 2450.15±669.8 g, and males represented 59.6% of the study sample.

During the study period, 25(6.5%) neonates had necrotizing enterocolitis (NEC), which was detected in 8 full-term neonates (2.1%) and 17 premature neonates (4.4%). The baseline characteristics of neonates according to the presence of NEC are shown in Table (1). In the premature neonate group, males represented 52.9% of Group I and 60.4% of Group II, whereas females represented 47.1% of Group I and 39.6% of group II, p:0.5. Low birth weight was detected in 94.1% of group I and 78.4% of group II, p:0.1, without significant difference between two groups regarding Apgar score at 5 minutes after birth; 8.88±1.1 in group I versus 8.82±1.4 in group II,p:0.8. need for respiratory support was significantly higher in group I(70.6% versus 47.8%,p:0.01) with highest rate of congenital heart disease in group I(47.1% versus 17.9%,p:006).

In addition, neonatal infection was present in all NEC cases(100% versus 80.6%), P:0.04. Anemia was significantly higher in group I(88.2% versus 38.1%,p:0.0001) and blood transfusion was higher in this group(76.5% versus 13.4%,p:0.0001).

There were no significant differences between two groups(I versus II) regarding presence of gestational hypertension, intrahepatic cholestasis of pregnancy, meconium aspiration syndrome, and presence of small for gestational age(SGA);(23.5% versus 20.1%,p:0.7),(0% versus 2.2%,p:0.5) and (0% versus 1.5%,p:0.6),(11.8% versus 9.7%,p:0.7) respectively. Use of formula for feeding was detected more frequently in neonates with NEC (94.1% versus 64.9%,p:0.01) with longer duration of antibiotic use in this group(15.5±9.8 versus 10.24±7.9,p:0.03).

In full-term neonates group, males represented 50% of group III and 59.9% of group IV, whereas females represented 50% of group III and 40.1% of group IV, p:0.5. Low birth weight was detected in 37.5% of group III and 20.7% of group IV, p:0.2, without significant difference between two groups regarding Apgar score at 5 minutes after birth; 8.12±1.7 in group III versus 9.10±1.1 in group IV,p:0.05. Need for respiratory support was significantly higher in group III(87.5% versus 48%,p:0.02), with the highest rate of congenital heart disease in group III(50% versus 20.3%,p:04).

In addition, neonatal infection was present in all NEC cases(100% versus 78.9%), P:0.04. Anemia was significantly higher in group III(75%versus 24.7%,p:0.001) and blood transfusion was higher in this group(37.5% versus 7.9%,p:0.004). There were no significant differences between the two groups(III versus IV) regarding the presence of intrahepatic cholestasis of pregnancy and meconium aspiration syndrome (0% versus 0.9%,p:0.7)and (0% versus 4.8%,p:0.5) respectively.

Use of formula for feeding was detected more frequently in neonates without NEC(63% versus 50%,p:0.4) with longer duration of antibiotic use in group III(12±7.2 versus 8.66±6.4,p:0.1). 25% of neonates who had NEC were SGA versus 7% in neonates without NEC,p:0.03, and gestational hypertension was detected more frequently in neonates with NEC(25% versus 5.7%,p:0.02).

Table 1. The relationship between NEC and demographic variables of the study population according to gestational age

Variable	Variable					
	Prematurity			Full term		
	Group I NEC(+)	Group II NEC(-)	p-value	Group III NEC(+)	Group IV NEC(-)	p-value
Gender Male Female	9(52.9%) 8(47.1%)	81(60.4%) 53(39.6%)	0.5	4(50%) 4(50%)	136(59.9%) 91(40.1%)	0.5
Low birth weight Present Absent	16(94.1%) 1(5.9%)	105(78.4%) 29(21.6%)	0.1	3(37.5%) 5(62.5%)	47(20.7%) 180(79.3%)	0.2
SGA Present Absent	2(11.8%) 15(88.2%)	13(9.7%) 121(90.3%)	0.7	2(25%) 6(75%)	16(7%) 211(93%)	0.03
5-minute Apgar score	8.88±1.1	8.82±1.4	0.8	8.12±1.7	9.10±1.1	0.05
Need for respiratory support Present Absent	12(70.6%) 5(29.4%)	64(47.8%) 70(52.2%)	0.01	7(87.5%) 1(12.5%)	109(48%) 118(52%)	0.02
Presence of congenital heart anomalies Present Absent	8(47.1%) 9(52.9%)	24(17.9%) 110(82.1%)	0.006	4(50%) 4(50%)	46(20.3%) 46(20.3%)	0.04
Neonatal infection Present Absent	17(100%) 0(0%)	108(80.6%) 26(19.4%)	0.04	8(100%) 0(0%)	179(78.9%) 48(21.1%)	0.04
Blood transfusion Present Absent	13(76.5%) 4(23.5%)	18(13.4%) 116(86.6%)	0.0001	3(37.5%) 5(62.5%)	18(7.9%) 209(92.1%)	0.004
Anemia Present Absent	15(88.2%) 2(11.8%)	51(38.1%) 83(61.9%)	0.0001	6(75%) 2(75%)	56(24.7%) 171(75.3%)	0.001
Meconium aspiration syndrome Present Absent	0(0%) 17(100%)	2(1.5%) 132(98.5%)	0.6	0(0%) 8(100%)	11(4.8%) 216(95.2%)	0.5
Intrahepatic cholestasis of pregnancy Present Absent	0(0%) 17(100%)	3(2.2%) 131(97.8%)	0.5	0(0%) 8(100%)	2(0.9%) 225(99.1%)	0.7
Gestational hypertension Present Absent	4(23.5%) 13(76.5%)	27(20.1%) 107(79.9%)	0.7	2(25%) 6(75%)	13(5.7%) 214(94.3%)	0.02
Feeding pattern Formula Breastfeeding	16(94.1%) 1(5.9%)	87(64.9%) 47(35.1%)	0.01	4(50%) 4(50%)	143(63%) 84(37%)	0.4
Duration of antibiotic use(day)	15.5±9.8	10.24±7.9	0.03	12±7.2	8.66±6.4	0.1

In the multivariate logistic regression analysis, the need for respiratory support (RR 4.2,95% CI 1.7-15.9, p=0.0001), presence of congenital heart anomalies (RR 2.4,95% CI 1.1-11.3, p=0.002), gestational hypertension (RR 3.4,95% CI 1.9-16.7, p=0.0001) transfusion of blood (RR 5.5,95% CI 1.5-12.4, p=0.0001), presence of anemia(RR 7.7,95% CI 1.9-20.2, p=0.0001) and SGA (RR 4.02,95% CI 1.3-11.7, p=0.0001 were factors that associated with the risk of progression NEC in full-term neonates, Table (2).

In the multivariate logistic regression analysis, need for respiratory support (RR 2.1,95% CI 0.9-6.9, p=0.04), presence of congenital heart anomalies (RR 3.2,95% CI 1.5-10.2, p=0.002), transfusion of blood (RR 9.5,95% CI 6.4-18.2, p=0.0001), presence of anemia (RR 7.3,95% CI 3.3-17.7, p=0.0001) and use of the formula for feeding (RR 5.4,95% CI 2.1-11.4, p=0.0001 were factors that associated with the risk of progression NEC in premature neonates, Table (3).

Table 3. Risk factors for NEC of premature neonates

Variable	RR b [CI 95%]	RR a [CI 95%]	P value
Need for respiratory support	2.6[0.8-7.8]	2.1[0.9-6.9]	0.04
Presence of congenital heart anomalies	4.07[1.4-11.6]	3.2[1.5-10.2]	0.002
Blood transfusion	12.9[6.1-20.3]	9.5[6.4-18.2]	0.0001
Anemia	12.2[2.6-17.2]	7.3[3.3-17.7]	0.0001
Use of formula	8.6[1.3-13.5]	5.4[2.1-11.4]	0.0001

4. Discussion

Necrotizing enterocolitis (NEC) represents a serious condition among neonates admitted to NICU, especially in severe cases with increasing evidence of worse long-term outcomes. Prevention of NEC, halting its progression, and reducing its complications represent the main goal of identifying risk factors for NEC. NEC was present in 6.5% of neonates admitted to NICU, which varies between studies due to the difference in inclusion and exclusion criteria and risk factors. There was a significant correlation between NEC and the presence of SGA only in full-term neonates, which might be explained by immature intestinal function, slow intestinal peristalsis, food residues that provide a good environment for bacterial growth, and immature microbiota, which lead to inflammation related to mucosal damage. This finding is in agreement with Ahle et al. (20). The result of the current study revealed that NEC was associated significantly with blood transfusion in full-term and premature neonates, compared with the control group, which might be related to inflammatory mediators during storage of red blood cells and the residual white blood cells, free hemoglobin, and red blood fragments which promote the occurrence of NEC. In addition, erythrocyte deformability decreased, oxygen affinity increased, and nitric oxide decreased, leading to loss of vasodilator activity and failure to improve intestinal microcirculation perfusion flow. This finding is in agreement with Lu et al. (21).

Anemia was associated significantly with NEC in premature and full-term neonates, which might be related to hypoxemic/ hypoperfused intestines and affecting the intestinal mucosal integrity of neonates. This finding is in agreement with Singh et al. (22) and Ahle et al. (20), which demonstrated an association between anemia and NEC only in premature neonates. The presence of congenital heart anomalies was associated significantly with the development of NEC in both premature and full-term neonates, which might be explained by intestinal hypo-perfusion mainly. This finding is in agreement with Lu et al. (21) and Ahle et al. (20). In addition, the use of the formula for feeding was associated significantly with the occurrence of NEC in premature neonates, which might be explained by the immature intestinal mucosa and higher osmotic pressure compared to breast milk, which increases the impact on intestinal function and incidence of NEC. This finding is in agreement with Daniel et al. (23).

There was a significant correlation between gestational hypertension and the development of NEC in full-term neonates, which might be related to placental insufficiency, fetal hypoxia, elevated levels of inflammatory cytokines, and increasing intestinal sensitivity. This finding is in agreement with Yang et al. (24). In contrast to the current study, March et al. (25) didn't find any correlation between gestational hypertension and the development of NEC. There were significant correlations between neonatal infection and oxygen therapy with the development of NEC in both premature and full-term neonates. These findings might be explained by direct and indirect damage to the intestinal mucosa and participation in the occurrence of NEC, and this is in agreement with Lu et al. (21). Use of antibiotics for longer duration was associated significantly with the development of NEC in premature neonates, which might be explained by disturbance of microbiota in the gastrointestinal tract and predisposing to NEC. This finding is in agreement with Alexander et al. (26).

There were no significant correlations between the Apgar score and the occurrence of NEC, which might be related to intensive care that was performed in high-risk pregnancies in our unit. In contrast to the current study, Ahle et al. (20) found a significant correlation between decreasing Apgar scores and the occurrence of NEC. There was no significant correlation between meconium aspiration and the development of NEC, and this finding is in agreement with Zheng et al. (27). In contrast to the current study, Lu et al. (21) demonstrated a significant association between NEC and the presence of meconium aspiration only in full-term neonates.

Lu et al. (21) found a significant correlation between sex, low birth weight, intrahepatic cholestasis of pregnancy, and development of NEC, which might be explained by the large sample size and performing it in multi-centre.

5. Conclusion

There is a significant prevalence of NEC in our health center, and the presence of anemia and blood transfusion represented the most important warning flags that may predispose to NEC in both full-term and premature neonates, in addition to the presence of other risk factors. In summary, clinical circumstances during pregnancy, around birth, and during the first days of life are critical for the development of NEC so that early initiation of protective measurement to reduce premature deliveries, reduce the use of formula and depend only on breast milk, and use of an antibiotic if necessary for limited duration of time are considered crucial to improve final outcome.

Declaration

Ethical Consideration

After discussing the study with the parents, all of them gave complete and clear informed consent to participate in the study.

Availability of data and materials

Most of the data was in the article, and other data can be asked from the corresponding author.

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