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Original Article

Necrotizing Enterocolitis in Preterm Neonates: Prognostic Factors and Outcome

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ABSTRACT

Necrotizing Enterocolitis (NEC) contributes significantly to a high neonatal death rate in Pakistan and other developing countries. A number of elements related to its development are modifiable and can be addressed. **Objectives:** To evaluate the frequency of NEC, its associated factors and outcome in preterm babies. **Methods:** This retrospective, cross-sectional study was conducted at Ziauddin University Hospital, Karachi. Medical records of admitted preterm newborns from 1st December 2020 till 1st December 2022 were reviewed and neonates meeting the modified Bell's diagnostic criteria ,with NEC stage II and III were included. Data pertaining to antenatal period, delivery and postnatal course of the disease were recorded . Data analysis were done using SPSS version-20 and results expressed as frequencies and percentages. Chi square test was applied with p-value statistical significance set at <0.05. **Results:** The prevalence of NEC was observed to be 7.1%. Male to female ratio was 1.6:1 with 84.5% of the neonates being low birth weight and culture-proven sepsis present in 44.8%. The mortality rate was 32.7%. Thrombocytopenia, hypotension, formula feeds, a positive blood culture and invasive ventilation were significant risk factors for mortality (p-value 0.01) **Conclusions:** Necrotizing enterocolitis has a high prevalence and mortality in preemies. Sepsis, formula feeding and a low birth weight adversely affect outcome. Early diagnosis and timely intervention can improve survival.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a serious life-threatening condition occurring in neonates and characterized by bowel ischemia, necrosis and multisystem organ failure. NEC is associated with increasing morbidity and mortality [1]. It is considered a common gastrointestinal emergency in newborns especially those born prematurely. The cause of this condition is multifactorial and functional immaturity of the intestine has been implicated in its pathogenesis [2]. Microbial dysbiosis plays an important role in the pathogenesis of NEC. Research studies have reported significant differences in gut microbiota composition between low birth weight and normal birth weight infants as well as between infants with and without NEC. The risk factors that have been reported in literature include prematurity, small for gestational age (SGA), hypoxic –ischemic injury, early and rapid advancement of enteral feeds, formula feeding and bacterial overgrowth [3]. However, among many causative factors, prematurity, low birth weight and formula feeding in preterm neonates are the most consistently recorded risk factors. Breast milk as compared to formula milk is nutritious so, it is recommended that enteral feeding with human milk be introduced as soon as possible to reduce the risk of infection throughout the body of neonates [4]. A confirmed

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diagnosis of NEC is based on the modified Bell's criteria, which includes clinical signs and symptoms like abdominal distension, vomiting, orogastric tube (OGT) residue and presence of at least one radiologic anomaly, such as pneumatosis intestinalis, gas in the portal vein, or pneumoperitoneum [1]. The prognosis and the management of affected neonates is considerably affected by the severity of NEC as indicated by Bell's stages II and III being present in neonates with proven or advanced NEC respectively [3]. Although the prevalence of NEC varies among centers, recent studies report up to 9000 cases in the United states every year with a mortality rate of 15% to 30% [5]. In a study by Sharma *et al.*, the frequency of NEC among preterm neonates was 8.3% [6]. Other studies have reported the rate of NEC-associated mortality to be greater than 10% overall and more than 25% for infants with NEC severe enough to require surgical intervention [7]. A study reported a prevalence rate of 26.8% for very low birth weight neonates with NEC and a very high mortality rate of 53.38% [8]. Therefore, it is emphasized that a timely diagnosis and management of NEC is imperative for better outcomes. A number of factors, some of which are debatable, increase a preemie's risk of acquiring the disease. As a result, developing novel strategies to stop the emergence and spread of NEC becomes difficult. In developing countries, there are only a few research studies regarding the local contextual elements involved in the development of NEC [9]. Multicenter research on a larger scale should be performed to develop efficient preventive, diagnostic and treatment strategies. Furthermore, the development of a national registry in this regard is imperative [10]. The rationale of our research was to evaluate the influencing factors of NEC in preemies and thus provide an insight into a better implementation of preventive strategies. Since premature births are common in our society, an effective treatment modality needs be adopted to reduce the prevalence of necrotizing enterocolitis and to reduce the burden of this condition on the already meagre resources [8].

METHODS

It was a retrospective cross-sectional research undertaken at the Ziauddin hospital . Records of premature babies admitted during 1st December 2020 till 1st December 2022 were reviewed and preemies with the confirmed diagnosis of necrotizing enterocolitis (NEC) who remained in the neonatal intensive care unit (NICU) for more than 72 hours were included .Only those neonates having NEC stages II and III were made part of the study. All records of preterm neonates with NEC having insufficient data, who were discharged before 72 hours of age, had abdominal distention or emesis at the time of admission, those with other gastrointestinal disorders e.g., meconium ileus, with congenital malformations were excluded. Neonates in whom a confirmed diagnosis of NEC was made were considered confirmed cases based on the Modified Bell's diagnostic criteria that includes the presence of clinical features e.g. vomiting, orogastric residue, abdominal distension , laboratory findings of thrombocytopenia , blood in stool and the presence of at least one radiologic abnormality, such as intramural bowel gas, portal venous gas ,or pneumoperitoneum. All preterm neonates diagnosed as having confirmed NEC were followed during the course of disease while they were admitted. Final outcome with regards to recovery , discharge , referral to other hospitals for treatment or death were recorded. ERC approval was sought for the study (Reference code: 6600223SEPED). The data were entered on a pre-designed proforma that recorded newborn factors such as gender, weight, gestational age, appearance, pulse, grimace, activity, respiration score (Apgar), mode of delivery, perinatal asphyxia, use of antenatal steroids, information regarding enteral feeding with human milk feed or formula as well as clinical features and treatment instituted whether conservative or surgical and the outcome were recorded. The proforma was pretested before actual study and necessary changes made to maximize the reliability and confidentiality of the data. Finally, the data were examined for completeness by the principal investigator. Data were entered and analyzed using SPSS version-20.0. Qualitative data were expressed as mean and standard deviation and quantitative data as frequencies and percentages. Chi-square was applied for categorical variables. p-value of <0.05 was taken as significant.

RESULTS

The frequency of NEC in our study was 7.1% , as 812 neonates were admitted in the neonatal intensive care unit (NICU) during the study period and 58 were diagnosed as having confirmed NEC. It was noted that 37 (63.8%) had NEC stage II A, 12(20.7%) NEC stage IIB, NEC stage IIIA was present in 6 (10.3%) and stage III B in 3 (5.2%). Out of the 58 neonates with NEC, 36 (62.1%) were male and 22 (37.9%) females, with a male to female ratio of 1.6:1. Majority of the newborns 41 (70.7%) were delivered through caesarian section. The mean age at initiation of signs and symptoms of NEC was 8.2 ± 4 (range 5-26 days). Average gestational age was 28.2 ± 3.2 weeks (27-36), 67% of them were < 32 weeks, the average weight was 1325 ± 260 grams (940 - 2250). In majority of newborns i.e. 32 (55.2%) enteral feeds were started within three days of admission. Average time of initiation of feed was 3.5 ± 1.72 days (2- 16 days). Distribution of the study population according to clinical characteristics is shown in table 1.

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Table 1: Clinical characteristics of preterm neonates with NEC

Characteristics	Range	N (%)
Birth weight (grams)	< 1000	5 (8.6)
	1100-1500	29 (50)
	1600-2000	12 (20.7)
	2100-2400	8 (13.8)
	>2400	4 (6.9)
Gestational age (weeks)	27-29	18 (31)
	30-33	31(53.4)
	34-36	9 (15.5)
Sepsis		26 (44.8)
Vaginal delivery		17 (29.3)
Formula feeding		39 (67.2)
Apgar score < 7 at 5 min		16 (27.6)
Antenatal glucocorticoid		42 (72.4)
Patent ductus arteriosus		4 (6.9)
Perinatal asphyxia		8 (13.8)
Mechanical ventilation		24 (41.3)
Umbilical arterial catheter		19 (32.8)
Exchange transfusion		4 (6.9)
H2 blockers use		16 (27.6)
Prolonged (≥5 days) first course of antibiotics		26 (44.8)
Blood transfusions		15 (25.9)
Respiratory distress syndrome		24 (41.4)
Thrombocytopenia		39 (67.2)
Maternal hypertensive disease		19 (32.8)
Polycythemia		11 (19)
Cyanotic congenital heart disease		5 (8.6)

Majority of the neonates i.e., 49 (84.5%) were low birth weight and 69.7% weighed less than 1500 grams, 18(31%) had respiratory distress syndrome (RDS) ,15 (25.9%) was transfused blood, Invasive ventilation was used in 24 (41.3%), while in 12 (20.7%) intravenous immunoglobulins were administered. The mean Apgar score at 1 and 5 minutes was 6.5 ± 2.1 (3-8) and 8.2 ± 2.8 (5-9) respectively. Table 2 shows the frequency of type of feeding in the study population.

Table 2: Distribution of the study population according to type of feeding

Type of enteral feed	NEC stage II	NEC stage III	Total N (%)
Human milk	13	1	14 (24.1)
Formula milk	21	4	25 (43.1)
Nil	6	1	7 (12.1)
Both	9	3	12 (20.7)
Total	49	9	58 (100)

Thrombocytopenia was present in 31(53.4%) neonates with NEC . Abdominal distention was the commonest symptom observed in 64%, followed by bilious vomiting in 36% while apnea was present in 32% and hypotension requiring inotropic support was recorded in 32.8% of the neonates. It was observed that in those neonates who expired, apneic episodes were present in 44% and hypotension requiring inotropic support in 84.2 %. Blood culture revealed bacterial growth in 26 (44.8%) neonates. Gram-negative bacteria were the commonest bacterial isolates in 23 (88.5%) with *Klebsiella* isolated in 11(42.3%), Acinetobacter in 6(23.1%), Pseudomonas aeruginosa in 4 (15.4) and Escherichia coli in 2 (7.7%). Gram -positive bacteria were isolated in only 3 (11.5%) blood culture specimens and staphylococcus aureus was the isolate in all of them. It was observed that low birth weight, advanced NEC stage, formula milk feeding, a positive blood culture, invasive ventilation, thrombocytopenia and hypotension were significantly associated with increased mortality in newborns (p-value 0.01 ,0.01, 0.01 ,0.02 ,0.01,0.01, 0.03 respectively). Thrombocytopenia was present in 15(78.9%) of the expired preterm babies with NEC and 94% of neonates with NEC stage III. Table 3 shows the general characteristics of preterm neonates who survived and those who expired.

Table 3: Characteristics of survival group versus expiry group of study population

Characteristics	Survived	Expired	p-value
Birth weight (grams)	2250 ±241	1678±315	0.01
Male	24	12	0.09
Gestational Age (weeks)	33.46± 2.35	30.65 ± 3.46	0.03
Age at NEC onset (days)	9.47 ±5.30	10.58±6.37	0.09
Perinatal asphyxia	15	3	0.71
H2 blocker	10	2	0.92
Blood transfusion	12	3	0.54
APGAR score			
1min	7.45 ± 1.82	6.98 ± 2.69	0.84
5min	8.72 ± 2.75	8.31 ± 4.46	0.18
Mechanical Ventilation	11	13	0.01
Culture- proven sepsis	18	8	0.02
Formula feed	19	7	0.01
Thrombocytopenia	16	15	0.01
NEC stage III	5	4	0.01
Inotropic support	3	16	0.03

Conservative treatment was employed in 49 (84.5%) neonates while 9 (15.5%) needed surgical intervention and the post-surgical expiry rate was 29%. The overall mortality rate was 32.7% i.e., out of a total of 58 neonates in the study population, 19 expired, 3 (5.2%) left against medical advice while 36(62.1%) were discharged.

DISCUSSION

NEC has the tendency for sudden progression to disseminated intravascular coagulation, hypotension and multi-organ failure. Research data on the prognosis of NEC in developing countries is scarce, although a number of prognostic elements of NEC are adaptable and connected to survival in newborns and therefore, if addressed can help prevent this condition [11]. The prevalence of NEC in our

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study population was 7.1%. Temere *et al.*, in their study from Ethiopia have reported a similar prevalence rate of 9.7% while Mekonnen *et al.*, observed a much higher prevalence of 25.4% though, Rees *et al.*, have reported a much lower NEC prevalence rate of 1.8% in developed countries [10, 12, 13]. In our study the survival rate of preemies with NEC was high i.e. 72.4% whereas research findings of Satardien *et al.*, reveal a survival rate of 44.2% [14]. The reason for a lower mortality rate in our study is explained by early diagnosis of the condition and prompt availability of pediatric surgical facility. The findings of our study highlight NEC staging to be an important prognostic element for a good outcome in NEC. We found that low birth weight and NEC stage III are greatly related to mortality. In the present study, 69.7% of the neonates with NEC were less than 1500 grams and stage III were present in 9(15.5%). A number of research observed NEC and its mortality to be strongly related to low birth weight [4, 5]. This is so because low weight at birth is connected to a weak immune function and therefore, a greater chance of acquiring infection [6]. We observed the frequency of enteral feeding using breast milk was low in the study population i.e., 43%, this was due to the development of prematurity related complications. A number of studies have highlighted the role of exclusive human milk enteral feeding to be protective against NEC [4, 10]. Blood culture proven sepsis was present in 26 (44.8%) of our study population. *Klebsiella pneumoniae* was the predominant organism in 42.3 % of neonates with positive blood culture, followed by Acinetobacter species in 23.1 % while staphylococcus aureus was isolated in only 5.3%%. A previous local study has also reported infection with *Klebsiella* and other gram-negative organisms to be mainly responsible for causing NEC in preterm babies [15]. A study by Dong *et al.*, reported S. epidermidis to be the predominant organism causing sepsis in preterm newborns and it led to an approximately two-fold increase in the NEC prevalence [16]. We noted the prevalence of NEC to be higher in males as compared to females with a male to female ratio of (1.6:1). Our findings are similar to a research data from India, and another study from Karachi wherein all the neonates admitted with NEC were males [15, 17]. However, Siahaan *et al.*, observed a higher prevalence of NEC in females and 3.1-fold higher risk of mortality [18]. These differences in findings could be due to variable geographical and sociodemographic factors involved. In the present study thrombocytopenia was related to a high chance of death with NEC, being present in 78.9 % of expired neonates (p-value 0.01). A number of studies have reported thrombocytopenia to be clearly connected with an advanced stage of NEC as it signifies intestinal ischemia and has been documented as a clear prognostic factor in affected neonates [2, 7]. Similarly, in our study 94 % of preterm babies with NEC stage III had a decreased platelet count. In concert with findings of other studies [19, 20], we found apnea, use of mechanical ventilation and decreased blood pressure requiring inotropic medication to be an important prognostic determinant of mortality. We noted that in neonates who expired, 44% had apnea and 84.2% had hypotension requiring inotropic support. The rate of invasive ventilation was higher i.e., 68.4% in neonates who expired. This might be due to an advanced stage of NEC being present in these neonates. A number of studies have reported conservative treatment to yield a higher survival rate than surgical intervention in preemies with NEC [21, 22]. Similarly, in our study, 84.5% neonates were treated conservatively while laparotomy was performed in 15.5% of the study population and the post-surgical expiry rate was only 29%. Thyoka *et al.*, and Kastenberg *et al.*, have reported a mortality rate as high as 50% after surgical treatment [2, 23].

CONCLUSIONS

In our study, high prevalence of NEC in preemies (7.1%) and death rate of 32.7% was recorded. Low birthweight, sepsis formula feeding and thrombocytopenia were linked to mortality. It is necessary to address risk factors associated with NEC and positively affect long term outcome in preterm babies.

Conflicts of Interest

The authors declare no conflict of interest.

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