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FREQUENCY OF NECROTIZING ENTEROCOLITIS IN PRETERM NEONATES AND THEIR OUTCOME DURING HOSPITAL STAY

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Abstract:

Background: *Neonatal necrotizing enterocolitis [NEC], characterized by intestinal necrosis and pneumatosis intestinal, is the most common gastrointestinal emergency in the premature newborns[1]. The disease has an incidence rate of 2 to 5% in premature infants. The incidence rate increases to 13% in those weighing 1,500 gram at birth. NEC has a mortality rate of 10 to 55%.*

Objective: *To determine the frequency of necrotizing enterocolitis in preterm neonates along with their outcome during stay in hospital.*

Methods: *All premature newborn with morbidity admitted at Neonatal Intensive Care Unit [NICU] the Children Hospital, PIMS, Islamabad were screened for enrolment. A total of 156 premature newborn who fulfilled the inclusion criteria were enrolled in the current study. The duration of study was 6 months. At the time of enrolment, demographic characteristics of all the enrolled babies were obtained and noted on the proforma specially designed for the study. Delivery complications, enteral feeding status and resuscitation at birth were also noted. Each baby was assessed for the diagnosis of NEC. Those who were diagnosed to have NEC where then followed for outcome. The outcome of study was either discharged [n=35] or died [n=12] during the hospital stay.*

Results: *During the study period a total of 156 babies were enrolled. Out of 156 babies, 47 [30.1%] babies were diagnosed to have NEC. The mean [SD] age of babies with NEC in this study was 7.8 [±4.1] days. Out of 47, 29 [62.0%] babies were aged up to 8 days. Out of 47 babies with NEC, 27 [57.0%] babies were male. Out of 47 babies with NEC, 26 [55.3%] babies were residence of urban areas. The mean [SD] gestational age was 32.1 [±3.4] weeks. Out of 47 babies with NEC, 30 [63.8%] babies with NEC had gestational age of 32 weeks or more. The mean [SD] weight was 1,813.7 [±283.4] grams. Out of 47 babies with NEC, 29 [61.7%] babies had weight less than 2,000 grams. Out of 47 babies with NEC, 28 [59.6%] babies with NEC were fed on formula milk. Out of 47 babies with NEC, 36 [76.6%] mothers had complications during the time of delivery. Out of 47 babies, 28 [60%] mothers had PROM. Out of 47 babies with NEC, 18 [38.3%] babies had hypoxic ischemic encephalopathy. Out of 47 babies with NEC, 28 [59.6%] babies with NEC were resuscitated at the time of birth. Out of 47 babies with NEC, 18 [38.3%] babies showed complete resolution, 11 [23.4%] babies showed partial resolution with residual disability, 6 [12.8%] babies with NEC showed no improvement whereas 12 [25.6%] babied died during their stay in the hospital.*

Conclusions: *Our study shows that out of 156 babies admitted and enrolled in our study, 47 [30.1%] were diagnosed to have NEC. Out of these 47 babies with NEC, 35 [74.4%] survived with 18, 11 and 6 babies showed complete resolution, partial resolution with residual disability, and no improvement respectively, while 12 [25.6%] were died during their hospital stay. However, there is a need to conduct further research including a multi-centre, large sample size study to investigate the burden of NEC in Pakistan.*

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INTRODUCTION:

Neonatal necrotizing enterocolitis [NEC], characterized by intestinal necrosis and pneumatosis intestinal, is the most common gastrointestinal emergency in the premature newborns. The disease has an incidence rate of 2 to 5% in premature infants. The incidence rate increases to 13% in those weighing 1,500 gram at birth. NEC has a mortality rate of 10 to 55%[1].

The triad of neonatal intestinal ischemia, microbial colonization of the gut, and excess protein substrate in the intestinal lumen associated with oral formula feeding seems to be a prerequisite in the pathogenesis of NEC[2]. It is estimated that disease affects up to 15% of premature infants and around 7% of full term neonate admitted to neonatal intensive care unit [NICU][3].

Outbreaks have been related to pathogens usually absent in the normal intestinal flora of the neonate, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Salmonella* spp. *Pseudomonas aeruginosa*, *Clostridium* spp., coagulase negative *Staphylococci*, [methicillin-resistant] *Staphylococcus aureus*, *Candida glabrata*, coronavirus, enterovirus, and rotavirus[4].

Incidence of NEC declines with increasing gestational age and low gestational age is the main single risk factor for NEC[5]. A recently published study by Zaidi and colleagues from Karachi, Pakistan reported out of 191 babies enrolled during the study period, 16 [8.3%] had necrotizing enterocolitis[6]. Enteral feed provides necessary substrate for proliferation of enteric pathogens. Hyperosmolar formula or medications may alter the mucosal damage. Human milk with the benefit providing immune protective as well as local growth promoting factors significantly lowers the risk of NEC. Moreover, enteral Immunoglobin A [IgA] and Immunoglobin G [IgG] feed also decreases the risk of NEC[7]. H2 Blocker therapy is associated with high rate of NEC[8]. Keeping in mind the neonatal mortality rate and morbidity in terms of complications due to NEC, it is very important to address these patients with early diagnosis, monitoring and timely management. We planned this study to determine the frequency of necrotizing enterocolitis in neonates along with their outcome during stay in hospital.

MATERIAL AND METHODS:

A descriptive, case series was conducted in the neonatal intensive care unit [NICU], Children Hospital, Pakistan Institute of Medical Sciences [PIMS], Islamabad over the period of six months from October 2012 to April 2013. All preterm babies admitted to the neonatal intensive care unit [NICU] screened for enrolment. A total of 156 preterm babies neonates admitted to NICU and who fulfilled the inclusion criteria were enrolled in this study. The sample size was estimated by using the World Health Organization [WHO] sample size calculations. The confidence interval level was considered at 95% and participating population was taken as 15%[3]. By considering the absolute precision at 8%, the required sample size was 156 babies. A purposive [non-probability] sampling technique was used to select cases. All the preterm babies with any morbid condition admitted in NICU of both gender. Informed consent given by parents/ guardian. Babies with gross congenital anomalies and gut anomalies having abdominal distension were excluded.

Operational Definition:

Necrotizing Enterocolitis:

Diagnosis was clinical by observing abdominal distension, brownish greenish nasogastric [NG] tube aspiration or emesis and blood in stool. Radiological findings were also considered for diagnosis of NEC. Supine abdominal radiographs are the mainstay of diagnosis. If NEC is suspected clinically, or there is concern on supine films, then an additional cross-table lateral or left-lateral decubitus film should be obtained:

- Dilated bowel loops [often asymmetrical in distribution]
- Loss of the normal polygynal gas shape
- Bowel wall edema with thumb printing
- Pneumatosis intestinalis [intramural gas]
- Portal venous gas
- Pneumoperitoneium secondary to perforation:
- Air on both sides of bowel [Rigler sign]
- Air outlining the falciform ligament [football sign].

Premature: Babies having gestational age less than 37 weeks.

Outcome:

It was assessed in the form of complete resolution, partial resolution with residual disability, no improvement or death from neonatal intensive care unit of the Children Hospital, PIMS hospital.

Data was collected through a structured proforma especially designed for this study. Permission was taken from the Hospital Ethics Committee before the commencement of the study. An informed consent was taken from the parents/ guardian of babies who fulfilled the inclusion criteria and were enrolled in the study.

The demographic characteristics such as gender, age of the baby at the time of presentation and place of residence [rural or urban] of every enrolled baby were collected and noted on the proforma. Furthermore, information about the gestational age of

the baby, weight, and status of enteral feeding with type of feeding [breast feeding or formula] were also collected. Information about delivery complications, premature rupture of membranes [PROM], hypoxic ischemic encephalopathy and resuscitation at birth was also collected and noted on the proforma. Babies with gross congenital anomalies or babies with gut anomalies having abdominal distension were not enrolled in the study.

The diagnosis of NEC was done by observing abdominal distension, brownish or greenish NG tube aspiration or emesis and blood in stool. Radiological findings were also considered for diagnosis of NEC. Supine abdominal radiographs are the mainstay of diagnosis. If NEC is suspected clinically, or there is concern on supine films, then an additional cross-table lateral or left-lateral decubitus film was obtained. The severity of the disease was graded according to Bell's scoring system. The outcome was assessed in the form of complete resolution, partial resolution with residual disability, no improvement or death from neonatal intensive care unit. All the enrolled babies were followed till we reach the outcome point, that is, either discharge from the hospital or death during their hospital stay.

Data were analyzed by using software SPSS version 18. The descriptive analysis was carried out and reported as mean with standard deviation [SD] and median for continuous variables such as age at the time of presentation, weight and gestational age. For categorical variables such as gender, place of residence, status of enteral feeding with type of feeding [breast feeding or formula], delivery complications, PROM, hypoxic ischemic encephalopathy, resuscitation at birth, diagnosis of NEC and outcome of NEC, frequencies and percentages were calculated and reported.

RESULTS:

During the study period a total of 156 premature babies were enrolled in the current study. Out of 156 babies, 47 [30.1%] babies were diagnosed to have NEC while 109 [69.9%] did not have NEC. The age distribution of babies with NEC is shown in Table 1.

Table 1: Age distribution of babies with NEC [n=47]

	No. of babies	%age
Age [in days]		
Mean ± SD	7.8± 4.1	
Median	8.0	
Range [min - max]	1.0 - 17.0	
Age categories		
Less than 8 days	29	61.7%
8-14 days	14	29.8%
≥15 days	4	8.5%

Out of 47 babies with NEC, 27 [57.0%] babies were male whereas 20 [43.0%] were females. The male to female ratio in our study was 1.35: 1.0. Out of 47 babies with NEC, 26 [55.3%] babies were residence of urban areas whereas 21 [44.7%] were living in rural communities.

GESTATIONAL AGE: The distribution of gestational age of babies with NEC in our study was as follow. The mean [SD] gestational age was 32.1 [±3.4] weeks with median of 33.0 weeks. The lowest gestational age of baby with NEC was 28 weeks while the highest gestational age was 35 weeks. Out of 47 babies with NEC, 30 [63.8%] babies with NEC had gestational age of 32 weeks or more, whereas 17 [36.2%] babies with NEC were less than 32 weeks of gestational age.

Table 2:Distribution of weight of babies with NEC [n=47]

	No. of babies	%age
Weight [in grams]		
Mean	1813.7	
Standard deviation	±283.4	
Median	1850.0	
Range [min - max]	1600.0 – 2200.0	
Weight categories		
Less than 2000 grams	29	61.7%
2000 to 2200 grams	18	38.3%

Out of 47 babies with NEC, 29 [61.7%] babies had weight less than 2,000 grams while 18 [38.3%] had weight between 2,000 and 2,200 grams.

ENTERAL FEEDING STATUS: The distribution of status of enteral feeding that out of 47 babies with NEC, 28 [59.6%] babies with NEC were fed on formula milk, while 19 [40.4%] babies with NEC were fed on breast milk. Out of 47 babies with NEC, 36 [76.6%] mothers had complications during the time of delivery, whereas 11 [23.4%] mothers did not have any delivery complications. Out of 47 babies, 28 [60%] mothers had PROM, whereas 19 [40%] mothers did not have PROM. Out of 47 babies with NEC, 18 [38.3%] babies had hypoxic ischemic encephalopathy while 29 [61.7%] did not have hypoxic ischemic encephalopathy. Out of 47 babies with NEC, 28 [59.6%] babies with NEC were resuscitated at the time of birth whereas 19 [40.4%] were not resuscitated at the time of birth.

OUTCOME: Out of 47 babies with NEC, 18 [38.3%] babies showed complete resolution, 11 [23.4%] babies showed partial resolution with residual disability, 6 [12.8%] babies with NEC showed no improvement whereas 12 [25.6%] babied died during their stay in the hospital.

DISCUSSION:

Necrotizing entrocolitis is one of the most common gastrointestinal emergencies in the newborn. Despite three decade of advances in neonatal care and significant clinical and basic science investigation, its etiology remains incompletely understood. In addition to this there is lack of consensus about specific treatment strategies and morbidity and mortality remain high particularly in developing countries. However, availability of exogenous surfactant and improved methods of respiratory support in the neonatal intensive care units in many developing countries, the survival of premature and low birth weight babies has also improve in developing countries. Nevertheless, as NEC is mainly a disease of premature and low birth weight babies, therefore, these units in developing countries are nowadays have seen a greater number of premature babies with NEC[9].

The current study was carried out to determine the frequency of necrotizing entrocolitis in babies and their outcome during their stay at neonatal intensive care unit [NICU], the Children Hospital, PIMS, Islamabad. A total of 156 babies admitted to NICU who fulfilled the inclusion criteria were enrolled. Out of 156 babies, 47 [30.1%] babies were diagnosed to have NEC while 109 [69.9%] did not have NEC. The mean [standard deviation] age of babies with NEC in this study was 7.8 [±4.1] days. The median age of babies with NEC was 8 days. The youngest baby was 1 day old while the eldest baby was 17 days of age. Out of 47, 29 [62.0%] babies were aged up to 8 days, while 14 [30%] were aged between 8 days and 14 days. Four [9%] babies were aged 15 day or more. Out of 47 babies with NEC, 27 [57.0%] babies were male whereas 20 [43.0%] were females. Out of 47 babies with NEC, 26 [55.3%] babies were residence of urban areas whereas 21 [44.7%] were living in rural communities. The mean [SD] gestational age was 32.1 [±3.4] weeks with median of 33.0 weeks. The lowest gestational age of baby with NEC was 28 weeks while the highest gestational age was 35 weeks. Out of 47 babies with NEC, 30 [63.8%] babies with NEC had gestational age of 32 weeks or more, whereas 17 [36.2%] babies with NEC were less than 32 weeks of gestational age. The mean [SD] weight was 1,813.7 [±283.4] grams with median of 1,850.0 grams. The lowest weight of the baby with NEC in the current study was 1,600.0 grams while the highest weight was 2200.0 grams. Out of 47 babies with NEC, 29 [61.7%] babies had weight less than 2,000 grams while 18 [38.3%] had weight between 2,000 and 2,200 grams. Out of 47 babies with NEC, 28 [59.6%] babies with NEC were fed on formula milk, while 19 [40.4%] babies with NEC were fed on breast milk. Out of 47 babies with NEC, 36 [76.6%] mothers had complications during the time of delivery, whereas 11 [23.4%] mothers did not have any delivery complications. Out of 47 babies, 28 [60%] mothers had PROM, whereas 19 [40%] mothers did not have PROM. Out of 47 babies with NEC, 18 [38.3%] babies had hypoxic ischemic encephalopathy while 29 [61.7%] did not have hypoxic ischemic encephalopathy. Out of 47 babies with NEC, 28 [59.6%] babies with NEC were resuscitated at the time of birth whereas 19 [40.4%] were not resuscitated at the time of birth. Out of 47 babies with NEC, 18 [38.3%] babies showed complete resolution, 11 [23.4%] babies showed partial resolution with residual disability, 6 [12.8%] babies with NEC showed no improvement whereas 12 [25.6%] babied died during their stay in the hospital. Our findings are comparable to other studies. However, it has been observed that the frequency of NEC varies significantly between various centers even within the same country and is inversely related to degree of prematurity.

There are, nevertheless, very few reports about the frequency of NEC from the developing countries. This may be due to either under reporting or high rate of early neonatal death before NEC can develop or a truly low frequency of NEC. In a study over 21 months in a big maternity hospital in Kuala Lumpur, Malaysia, the frequency of NEC was reported to be 2.4 per 1000 live birth and 2.7 per neonatal admission

[10].

In a study over 10 year period in Indian Kashmir's major neonatal unit, the frequency of NEC was reported as 1% of all live birth and 1% of all the neonatal admission [11]. Some developing countries reported a much higher rate as 5 % of the neonates admitted to NICU diagnosed to have NEC[12].

The frequency of NEC, however, varies in western counties. In Canada, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network reported gestational age specific mean incidence of NEC of 3% to 11% between 1997 and 2000[13] and 5% to 15% between 2003 and 2007[14]. Other developed countries also reported similar frequency of NEC in their study population [15-17].

A hospital based study was conducted to determine the frequency of NEC among preterm or low birth weight babies in Canada between January 2007 and December 2008. Two hundred and eighty-two preterm and or low birth weight babies were admitted during the study. Their gestational age and birth weight [mean ±SD] were 28.2 ±2.7 weeks and 1,031 ±290 g, respectively. Out of 282 infants, 23 [8.2%] of preterm infants were diagnosed to have NEC at their centre [18].

A hospital based study from Texas; USA was carried out at two centers to determine the frequency of NEC among preterm and low birth weight babies. The investigators enrolled 866 infants with birth weight of less than 1,500 grams. They found that out of 866, 86 [10%] babies had NEC who were admitted at both the centers[19].

On the other hand, recently a population based cohort study in Canada with an objective to determine the frequency of NEC among a cohort of preterm babies [less than 34 weeks] carried out by Yee WH and colleagues. They enrolled 16,669 preterm infants from January 2003 to December 2008. They found that out of 16,669, 858 [5.1%] infants had NEC[20].

In Australia, in New South Wales, a hospital based study was conducted between 1986 and 1999. The authors enrolled 1,655 infants from the participating centers during the study period. Out of 1,655 babies, NEC was diagnosed in 127 [7.7%] babies[21].

Nevertheless, NEC is uncommon in countries where prematurity rate is low such as Japan and Sweden[22]. In USA the frequency of NEC in neonatal units is reported to be 1-3 per 1,000 live births of which more than 90% of all cases occur in preterm infants[23]. In United Kingdom [UK] the overall frequency of NEC is reported to be 0.23 per 1,000 live births increasing to 2.1/baby admitted to a neonatal unit[24].

The neonatal mortality is very high in Pakistan as 54 per 1,000 live births with a high proportion of preterm and low birth weight babies. Prematurity and its complications are the major cause of mortality in newborn in Pakistan and majority of these deaths occur within 24 hours of life. At the same time more than 60% of deliveries are being conducted at home in Pakistan. Therefore, majority of these newborns died even reaching the hospital [25]. With a higher preterm births and higher mortality in premature babies with first 24 hours of live in Pakistan, therefore, a smaller proportion of preterm newborn who survive the critical period of first 24 hours, reaches the hospital. However, these preterm babies have already developed complications including NEC. Therefore, we have seen a higher frequency of NEC at our centre compared to other centers around the world. However, there is a need to conduct further studies to explore the causes of the higher frequency of NEC at our center.

In the current study out of 47 newborn diagnosed to have NEC, 35 [74.4%] survived and discharged from the hospital. However, 12 [25.6%] died during their hospital stay. Mortality rate from NEC varies between 10% and 30% in developed countries, despite the improvement in neonatal intensive care and increase in the overall survival of critically ill premature babies[26]. On the other hand, in the developing countries the mortality due to NEC can reach more than 50%. Most deaths occur in extremely low birth weight and growth restricted babies who frequently develop severe disease [27].

The two major risk factors for NEC are: prematurity and enteral [formula] feeding. The highest incidence of NEC is seen in premature babies. It is thought to be due to the immaturity of intestinal barrier function and digestion. Deficiency of intestinal immune defense systems and poor gut motility are also considered as major factors [27]. Therefore, to reduce the frequency of NEC, it is pertinent to carry out interventions for the prevention and for the better management of premature babies at our centre. Research has shown that a regular intake of iron supplements during pregnancy has a positive effect on prematurity and birth weight [28].

Research has shown that 90 to 95% of infants who develop NEC have been enterally fed. Feeding besides increasing direct osmotic injury to the gut mucosa alters splanchnic blood flow increasing the risk of ischemic injury. Feeding also increases bacterial growth and fermentation within the gut[29]. Babies fed on formula milk are at much greater risk of developing NEC than those who are exclusively fed on breast milk. Formula milk is devoid of immune-protective factors such as secretory IgA and there is evidence that formula milk alters bacterial gut colonization and may also induce inflammation in the gut mucosa[30]. On the other hand, the rate of

exclusive breastfeeding is low in Pakistan and only 37% of babies less than 6 months are exclusively breastfed [25]. There is a need to formulate and implement interventions by involving the mass media to improve the breastfeeding rate in Pakistan.

The ideal of course would be to prevent the occurrence of NEC but no such definitive strategy is known. However, once NEC has developed the goal of management is to prevent progression of the disease and intestinal perforation and shock. Principles of medical management include discontinuing oral feeding, starting intravenous fluids, naso or oro-gastric bowel decompression and antibiotic therapy. Babies with NEC are usually made nil by mouth [NPO] for a variable period of time depending on the severity of disease on an arbitrary basis. Currently there is no evidence or consensus on how long feeds should be withheld in a given case, thus making any definitive recommendation problematic [9].

Conventionally the duration of NPO is 10 – 14 days. Some suggest early enteral feeds should be resumed gradually preferably with trophic feeding using breast milk. This is important and recommended in developing countries where total parenteral nutrition [TPN] is either not available or restricted to few centers. With UNICEF campaign for breastfeeding friendly hospital, early feeding with expressed breast/banked breast milk should be considered in NEC with careful monitoring instead of keeping babies NPO or on I/V fluids for long periods for which there is no clear evidence[9].

Parenteral antibiotics are widely used for the treatment of NEC but there is little evidence for guiding the choice of antibiotic or the duration of therapy. WHO book on children recommends use of ampicillin and gentamicin plus minus metronidazole[31]. Use of broader cover [e. g. Vancomycin and cefotaxime] in smaller infants [<1,000 g] particularly where no response is seen to standard regimes should be considered. Conventional duration of empirical antibiotic therapy is 7 – 14 days but again there is no evidence to support it. Consideration should be given to stopping antibiotic therapy early if the baby is tolerating oral feeds and is clinically improving. Use of narcotic analgesia [Morphine or Fentanyl] should be considered to relieve pain and discomfort associated with severe NEC. Supportive therapy should include cardiovascular [inotrope, volume], pulmonary [oxygen, ventilation] and hematological support [FFP, Platelets, Blood Transfusion][9]. We also used WHO's recommendation for the treatment of NEC in our patients with ampicillin and gentamicin plus minus metronidazole[31]. Supportive therapy such as pulmonary [oxygen, ventilation] and hematological support [FFP, Platelets, Blood Transfusion] was also part of the management of NEC in out sample. With a good diagnosis and prompt treatment we have seen a good response rate among NEC babies in terms of morbidity and mortality.

Approx. 20% to 40% of babies with NEC with pneumatosis intestinalis will require surgery. Consultation with a pediatric surgeon is essential once the diagnosis of NEC is considered. Absolute indication for surgery includes pneumoperitoneum [perforation], portal venous gas and failure of medical treatment, abdominal mass and stricture. Ideally, surgery should be performed after the development of bowel necrosis [as early in the disease the bowel is very fragile] but before perforation and peritonitis occurs [9].

There are two types of surgical procedures performed for NEC: laparotomy [resection of necrotic bowel, formation of enterostomy and mucosal fistula] and peritoneal drainage [PD]. The relative benefits of these methods are controversial. A meta-analysis comparing all clinical trials [none were RCT's] of PD and laparotomy for perforated NEC did not show which of the two techniques was most effective, but found the mortality associated with surgery to be 35-55%[32]. Research has shown that in unstable preterm infant with perforated NEC the outcome from PD was not statistically different from laparotomy [33].

Hence, there is a need to formulate strategies for better management of NEC and improve the overall survival rate of premature newborn in developing countries like Pakistan.

CONCLUSION:

To conclude, our study shows that out of 156 premature babies admitted and enrolled in our study, 47 [30.1%] were diagnosed to have NEC. Out of these 47 babies with NEC, 35 [74.4%] survived with 18, 11 and 6 babies showed complete resolution, partial resolution with residual disability, and no improvement respectively, while 12 [25.6%] were died during their hospital stay. However, there is a need to conduct further research not only at hospital level but also at community level to determine the exact burden of this disease in Pakistan. A multicenter study with large sample size would be an ideal study to investigate the burden of NEC in Pakistan. At the same time, there is a need to formulate and implement interventions to prevent and manage premature babies with NEC. Efforts should be made at the community level for the better management of all women who are at risk of premature delivery and also appropriate management to premature babies at the community levels in Pakistan.

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