Journal of Neonatal Surgery 2018; 7:42
DOI: 10.21699/jns.v7i4.802.

OPEN ACCESS

ORIGINAL ARTICLE

Short-term Outcome of Low Birth Weight Preterm Infants with Necrotizing Enterocolitis: A Prospective Cohort Study

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How to cite: Pan P. Short-term Outcome of Low Birth Weight Preterm Infants with Necrotizing Enterocolitis: A Prospective Cohort Study. J Neonatal Surg. 2018;7:42.

ABSTRACT

Aim: The purpose of this study was to analyze the nature of the disease, the surgical procedures, complications, and survival of preterm infants with necrotizing enterocolitis (NEC) from two tertiary care referral neonatal intensive units in central India. **Materials and Methods:** A prospective study of a cohort of 110 preterm neonates with gestational age <36 weeks and weight <1600 g infants diagnosed to have NEC were followed for 90 days. All the neonates were born between January 2015 and December 2017 and treated at two neonatal intensive care units. Infants with sepsis, congenital gastrointestinal anomalies, major cardiac problems, and intraventricular hemorrhage were excluded. **Results:** Mean gestational age in this cohort was 32.40 ± 3.87 weeks, and the mean age of NEC onset was 13.04 ± 3.54 postnatal days. There were 39 neonates with Stage 1, 45 with Stage 2, and 26 with stage 3 NEC. Pneumoperitoneum, positive paracentesis and progressive clinical deterioration were the indications for laparotomy. The most common complications were sepsis 97/110 (88.18%). Post-operative complications occurred in 22 (84.61%) infants, wound infection in 19 (73.07%), intestinal stricture in 9 (34.61%), wound dehiscence in 7 (26.92%), stoma stenosis in 3 (11.53%), ileostomy prolapse in 2 (7.69%), and burst abdomen in 1 (3.84 %). The overall 90-day survival rate was 87.27% (96/110), and the post-operative survival rate was 46.15% (12/26). The age of gestation, weight, and extent of the disease were the main risk factor for mortality. **Conclusion:** The short-term outcomes for Stage 3 NEC were associated with high morbidity and mortality. The outlook for infants with Stage 1 and 2 NEC was favorable.

Key words: Necrotizing enterocolitis; Post-operative complication; Surgery; Survival

INTRODUCTION

Necrotizing enterocolitis (NEC) is still the most common cause of gastrointestinal-associated morbidity and mortality in neonatal intensive care unit (NICU) [1]. Prematurity and low birth weight are the most consistently agreed risk factors [2]. The disease prevalence is approximately 9–14% of infants born below 1500g [3]. It typically occurs in the second to 3rd week of life in premature, formula-fed infants and is associated with high morbidity and mortality (20–45%) [4]. The pathogenesis is multifactorial and has often been linked to enteral feedings, bowel ischemia, and infectious sources [5]. The process is thought to be headed by an ischemic or toxic event that causes damage to the immature gastrointestinal mucosa and loss of mucosal integrity [6]. The initiation of enteral feedings allows the proliferation of bacteria, and damaged mucosa is invaded by gas-producing bacteria leading to sepsis, necrosis or perforation of the bowel [7].

The clinical manifestation of NEC reflects a heterogeneous disease process with some infants manifesting localized intestinal injury, while others presenting with diffuse involvement and fulminant necrosis of the intestines. The recent consensus is that the immature intestine of premature infants exists in a hyperactive state due to abnormal bacterial colonization, which triggers an inflammatory response and impairment of intestinal perfusion [8]. The study evaluated the short-term outcome of preterm infants with NEC at different stages of diseases.

MATERIALS AND METHODS

This was a prospective cohort study conducted at two tertiary care referral neonatal intensive units in cen-

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Submitted: 20-7-2018
Accepted: 5-9-2018
Conflict of interest: None
Source of Support: Nil

tral India. 110 preterms, gestational age <36 weeks, and weight <1600 g neonates with NEC were prospectively analyzed from January 2015 to December 2017. The study protocol was approved by the Institutional Review Board. Written informed consent was obtained from the patient's parents once the diagnosis of NEC is made. NEC stage was determined according to the modified Bell (Walsh and Kliegman) staging criteria [9]. The surgical approaches undertaken included surgical resection of the necrotic intestine, the creation of intestinal stomas, or peritoneal drainage. Infants with sepsis, congenital gastrointestinal anomalies, major cardiac problems, and intraventricular hemorrhage were excluded. Data collected included demographic information, clinical, nutritional, laboratory, and radiological. Surgical and histopathology results of operated NEC cases were documented. Infectious and wound complications were evaluated. The requirement of mechanical ventilation, total parental nutrition, time to achieve full enteral feeds, length of stay, and survival to 90 days were analyzed.

RESULTS

There were 67 boys in this study with a mean gestational age of 32.40 ± 3.87 weeks. Mean weight at birth was 1106.6 ± 208.42 g and postnatal age at the onset of NEC was 13.04 ± 3.54 days. Maternal and neonatal data of enrolled neonates are shown in Table 1. There were 39 neonates with Stage 1, 45 with Stage 2, and 26 with Stage 3 NEC. Increased gastric residuals and abdominal distension were the initial signs (n = 103, 93.63%) of cases. The most frequently observed symptoms of NEC were: Abdominal distension (n = 107, 97.27%), pre-feeding residuals/gastric retention (n = 106, 96.36%), impaired elimination of stool (n = 79,71.81%), elevated C-reactive protein (n = 70,63.63%), and radiographic signs (n = 65,59.09%). Abdominal wall erythema was encountered in n = 38,34.54% of the patients and intestinal obstruction with absent passage of stools in n = 21,19.09%.

Laboratory findings were nonspecific. Organisms isolated in blood and peritoneal fluid (n = 97, 88.18%) were coagulase-negative staphylococci - 39.17%, *Staphylococcus aureus* - 16.49%, *Klebsiella sp.* - 19.58%, *Escherichia coli* - 13.40%, and *Enterobacter sp.* - 7.21%. Yeasts constituted 4.12% of all cases. An abdominal X-ray film was the mainstay of diagnosis. On plain radiograph generalized intestinal dilatation was seen in 81 (73.63%) patients, pneumoperitoneum in 13 (11.81%) (Figure 1a), fixed dilated intestinal loops in 8 (7,27%), pneumatosis intestinalis in 5(4.54%) (Figure 1b), gasless abdomen in 5 (4.54%), and portal venous gas in 2 (1.81%).

Absolute indication for laparotomy was pneumoperitoneum (n = 13), and relative indications included

Table 1: Maternal and neonatal characteristics in neonates with NEC

Parameters	Mean±(SD)	n (%)
Maternal data		
Age (years)	31.6±4.73	
Maternal hypertension		18 (16.36)
Maternal diabetes		9 (8.18)
Preeclamsia		19 (17.27)
Antepartum hemorrhage		23 (20.90)
Antenatal corticosteroid		33 (30.0)
Mode of delivery (vaginal)		86 (78.18)
Neonatal data		
Gestational age (weeks)	32.40±3.87	
Birth weight (g)	1106±208.42	
Gender (Male)		67 (60.90)
Clinical data at the time of delivery		
Apgar score at 1 min≤5		39 (35.45)
Apgar score at 5 min≤5		31 (28.18)
Use of resuscitation drugs		19 (17.27)
Use of surfactant		47 (42.72)
Mode of feeding		
Breast	69	62.72
Formula	41	37.27
NNEC clinical course		
Age of onset (days)	13.04±3.54	
Age at first feed (days)	4.16±2.6	
Vasopressor use		37 (33.63)
Mechanical ventilation		73 (66.36)
Positive blood culture		97 (88.18)
Parental nutrition		87 (79.09)
Feed resumed in stage 1 (days)	10.52±1.32	
Feed resumed in stage 2 (days)	15.7±3.26	
Feed resumed in stage 3 after operation (days)	11.03±3.23	
SD: Standard deviation		

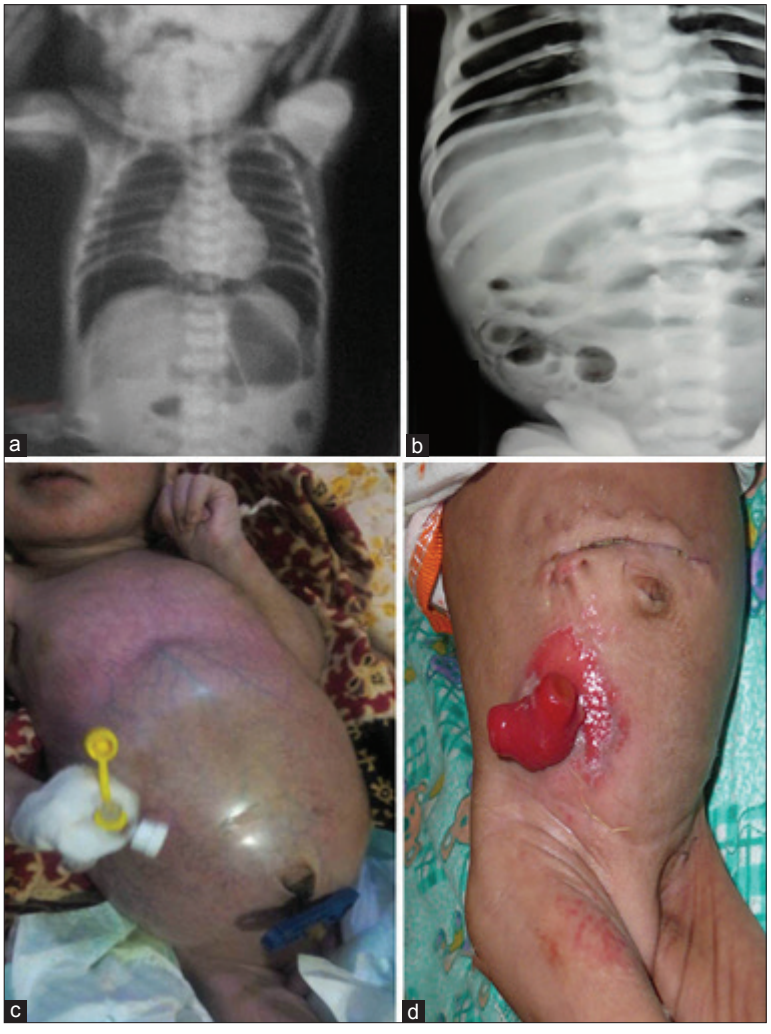

Figure 1: (a) X-ray showing pneumoperitoneum. (b) X-ray showing pneumatosis intestinalis. (c) Clinical photograph showing fixed abdominal mass and erythema. (d) Clinical photograph showing ileostomy prolapse

progressive clinical deterioration (n = 7) and positive paracentesis (n = 6). Table 2 shows the attributes of surgical patients. Perforation was found during the operation in 19 (73.07%) neonates, detected preoperatively in 13 neonates. Multifocal disease was found in 19 (73.07%), 4 (15.3%) had localized, and 3 (11.5%) was pan-intestinal. There were 16 neonates with only small bowel involvement, a combination of small and large bowel involvement in 8, and only large bowel involvement in 2. The ileum was the most commonly affected location (n = 24, 92.30%). As for the surgical approaches, enterostomy creation with necrotic bowel resection was the initial procedure in 19 patients. In 4 neonates, enterostomy without resection of gut was performed (2 jejunostomies and 2 transverse colostomies). Three children underwent laparotomy and simple drainage for pan-intestinal involvement with near total intestinal compromise (Table 3).

The most common post-operative complications were sepsis (n = 20, 76.92%). Other surgical complications are shown in Table 4. The median length of survival of the 14 deaths after surgery was 9 days (range 3–17). Three children died within 3 days of surgery. The cause of death was mainly attributed to pan intestinal NEC in these neonates. The remaining death resulted from sepsis, severe short bowel effects, respiratory distress syndrome, and multiple organ failures (Table 4).

The intestinal stricture was found in 9 surviving patients who underwent initial ileostomy. Eight patients who were conservatively managed initially from Stage 2, developed intestinal stricture and obstruction and underwent laparotomy with resection of stricture segment and anastomosis at age ranged from 43 to 51 days. The commonly affected sites were distal ileum, ascending colon, and transverse colon.

The length of stay in NICU was 37–53 days in Stage 1, 49–57 days in Stage 2, and 63–81 days in Stages 3. The average time of enterostomy reversal in this study was 97 days (range, 61–115 days) after primary laparotomy. The overall 90-day survival rate was 87.27%

Table 2: Demographics of 26 neonates undergoing operation

Surgical patients	Mean±SD
Gestational age (weeks)	29.01±1.433
Birth weight (g)	1042±61.359
Age at operation (days)	23.73±10.219
Weight at operation (g)	1169.46±138.538
SD: Standard deviation	

Table 3: Laparotomy findings and procedures applied for 26 surgical neonates

Operative findings	*n* (%)
Jejunoileal involvement	13 (50)
Ileal and colonic involvement	8 (30.76)
Only colonic involvement	2 (7.69)
Pan-intestinal	3 (11.53)
Multiple patch	19 (73.07)
Localized ileal patch	2 (7.69)
Operation performed	
Ostomy with resection	19 (73.07)
Ostomy without resection	4 (15.38)
Peritoneal drainage	3 (11.53)

and post-operative survival rate was 46.15%. There was no death occurred after stoma closure. Figure 2 showing the flowchart of 110 NNEC patients of this study.

DISCUSSION

Low birth weight and low gestational age are the most significant prognostic factor. Among the other important risk factors for developing NEC, the following are considered important: Low Apgar score [10], the need for surfactant application for respiratory distress syndrome [11], assisted ventilation, patent ductus arteriosus, late-onset bloodstream infections, enteral feeding, maternal hypertensive disease of pregnancy, placental abruption, absent or reversed end diastolic flow velocity, use of umbilical catheters, and hypotension requiring inotropic treatment [12]. In this study out of 14 deaths, five neonates were very preterm (28–31 weeks) and 9 were extremely preterm (27 weeks). In addition, nearly 80% had birth weights under 1kg who died.

Clinical and radiographic findings are often nonspecific in the initial period. The early and correct diagnosis of NEC is of utmost importance. According to the literature, bowel dilatation is present in 75–90% of cases in initial NEC, and focal or separated dilatation reflects more-advanced disease [13]. In our study, generalized intestinal dilatation was observed in 55.45% of neonates in Stage 1 and 2. In advanced NEC, the most common sign was pneumoperitoneum (11.81%). Persistent loop sign is the hallmark of impending perforation which was present in 30.76% of patients undergoing surgery. The presence of portal venous gas is associated with severe disease and higher mortality rates with the specificity and positive predictive value of 100% for intestinal necrosis [14]. However, pneumoperitoneum is considered an absolute indication for surgical treatment and is presented in only 50–75% of all patients with bowel perforation secondary to NEC [14]. In our study, pneumoperitoneum was found in 13 (50%) out of 26 neonates who underwent surgery.

Fixed abdominal masses and erythema of the abdominal wall which is strongly predictive of NEC are reported to present in 10% of patients [15], but in our series, we have found in 34.61% of the patients in Stage 3 (Figure 1c).

In patients with Stage 1 and Stage 2 NEC, the applied feeding program relied on parentral feeding, while oral feeding was prohibited, until patient started to thrive and tested for enteral feeding tolerance by 1-week increments of the amount of oral intake. Support for respiratory and cardiovascular failure was made. Frequent clinical examination and serial, abdominal radiography is required to identify the deterioration or progression of diseases. In Stage 1 of our study group feeding was resumed within 9–11 days and in Stage 2 feeding was resumed after 13–19 days. Recent studies reported that abdominal sonography could be used to evaluate bowel perfusion, viability, peristalsis, and fluid collections [16]. In this study, USG was used in 77 patients but could not predict the evolution of the disease.

Approximately 20–40% of cases with NEC require surgical intervention [17]. In our group of patients, $n = 26$ (23.63%) were surgically treated. The principal indication for operative intervention in NEC was perforated or necrotic intestine. Although the free intraperitoneal air was an absolute indication for surgical intervention, in this study, it was only seen in 50% (13/26). Paracentesis was utilized as an adjunctive in 31 patients but was positive in 6 patients. Other indications were erythema in the abdominal wall, gas in the portal vein, and clinical deterioration despite maximum medical therapy.

During operation, every effort needed was done to preserve maximum intestinal length. Resection of

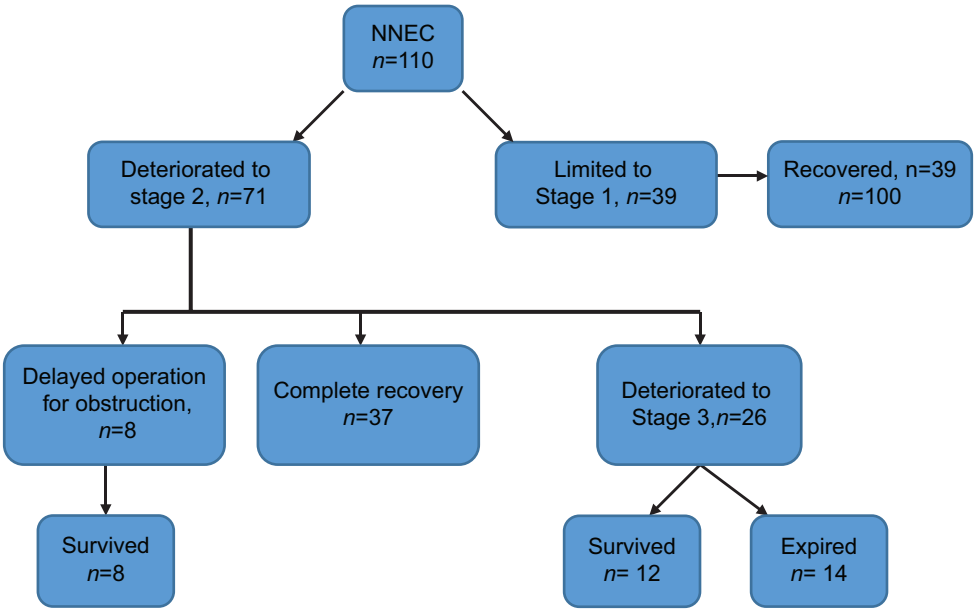

Figure 2: Flow chart showing the treatment and outcome of the 110 NNEC patients

Table 4: Post-operative complications and causes of deaths

Complications	*n* (%)
Sepsis	20 (76.92)
Wound infection	19 (73.07)
Intestinal stricture	9 (34.61)
Wound dehiscence	7 (26.92)
Pneumonia	5 (19.23)
Ileostomy stenosis	3 (11.53)
Ileostomy prolapse	2 (7.69)
Short bowel (18–24 cm)	2 (7.69)
Burst abdomen	1 (3.84)
Cause of death	
Pan necrosis	3 (21.42)
Sepsis with MODS	5 (35.71)
Extreme prematurity	4 (28.57)
Short bowel syndrome	2 (14.28)

necrotic bowel with enterostomy was performed in n = 19 (73.07%) of localized and multifocal cases. Literature has mentioned higher post-operative complication rates after NEC surgery, at times in excess of 50% [18]. The post-operative complication rate and stoma-related morbidity were high 73.07% in our series (Figure 1d). Wound dehiscence and wound infection remain troublesome complications, especially in wounds with stomas, where protecting the wound from stoma effluent requires diligent stoma care. The outcome of pan-intestinal NEC (NEC totalis) remained poor with a mortality rate of 100%. Sepsis was the most frequent complication seen in 39.09%. Prematurity, central line access and prolonged parenteral nutrition contribute to increased incidence of septic complication [19]. Intestinal strictures develop in 9–32% of patients who underwent the operation [20]. Stricture occurred after both medical and surgical treatment for NEC and in both functional and defunctionalized bowel. In this study, we found stricture in n = 9 (75%) of living child who had an initial operation and n = 8 (17.77%) of a patient with Stage 2 NNEC. A contrast study is advisable to rule out strictures or complete obstruction before restoration of intestinal continuity. Intestinal strictures result from collagen deposition; fibrosis and wound contraction over a variable period following an episode of acute inflammation. It is the reparative process following an acute decrease in flow through the intramural blood vessels [21]. Short bowel syndrome remains a major problem and has been reported as a surgical sequel in about a quarter of NEC patients [22]. NEC remains the most common cause of short bowel syndrome in neonates, with associated high mortality ranging from 6 to 47% and high morbidity [23]. In this series, only 2/26 patients (7.69%) had short bowel syndrome, and both could not be saved. Concerning short-term outcome; 96 patients (87.27%) passed hospital course, tolerated oral feeding and started to thrive (84 responded to medical therapy, and 12 after surgical intervention). Significantly higher success rate and lower morbidity and mortality rates were among patients who had a medical intervention as

compared to patients requiring surgical intervention. Murthy et al. [24] reported grave short-term outcomes after surgery for NEC, particularly for neonates born <28 weeks' gestation. The surgical outcome of NEC depends on the underlying variant pathogenesis in the population involved. It is possible that NEC exhibits different features, with a differing predictive result in different neonate populations [25, 26].

Limitations of our study include an inherent risk of selection bias. As some diseases, such as focal intestinal perforation, Hirschsprung enterocolitis, and milk protein allergy, share similar clinical features with NEC, misclassification bias is possible, although the pathological reports, operative notes, and radiographic images were assessed in these neonates for arriving the inclusion criteria. The strength was prospective nature of the study and close monitoring with no loss of patients to follow-up.

CONCLUSION

A high risk of developing NEC is closely associated with very low birth weight neonate. Bowel perforation in premature neonates with NEC is associated with lesser gestational age, lower birth weight, apnea, mechanical ventilation, and sepsis. There is no clear evidence-based consensus on the requirement of surgery, with the exception in the evidence of bowel perforation. Short-term outcomes for preterm neonates with surgical NEC in this study were accompanied by high mortality and complications rate. The outlook for neonates with Stage 1 and 2 NEC was favorable. Further studies are required to recognize the risk factors, preventive measures, and optimal timing of surgical intervention.

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