Factors affecting mortality in stage 3b necrotizing enterocolitis

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This study aimed to determine the factors that may affect the development of mortality in patients with stage 3b necrotizing enterocolitis (NEC). Between January 2005 and December 2012, patients with the diagnosis of stage 3b NEC who were surgically treated were enrolled in the study. Gestational age, birth weight, presence of hypoxemia history, major congenital heart diseases, enteral feeding, age at perforation, drainage type, operation, and laboratory findings were considered regarding their possible relationship with mortality. Thirty-one patients were enrolled in this study. Following treatment, 15 patients died, while 16 patients recovered and were discharged. Feeding type, high levels of prothrombin time (PT), activated partial thromboplastin time (aPTT), creatinine, and low platelet count, as well as need of inotropic support were associated with mortality. When the cut-off point of platelet level for mortality development in stage 3b NEC was calculated by receiver operating characteristic (ROC) curve, the cut-off point for thrombocyte level was found to be 110,000/μL, with 93.3% sensitivity and 87.5% specificity. Despite the innovations in newborn intensive care, the mortality rate of stage 3b NEC remains very high. Breastfeeding has a significantly positive impact on the survival of patients with NEC. Thrombocytopenia is the most important risk factor of mortality in stage 3b NEC.

Key words: necrotizing enterocolitis, intestinal perforation, primary peritoneal drainage, thrombocytopenia, mortality.

Necrotizing enterocolitis (NEC) is the most common life-threatening gastrointestinal system emergency among newborns, and is characterized by bowel necrosis and multisystem failure[1,2]. Although many clinical, experimental and epidemiologic studies have been conducted, the etiology of NEC is still unclear. Notwithstanding the innovations in newborn intensive care units, the morbidity and mortality rates of NEC remain very high[3].

Based on the clinical and radiological signs, modified Bell's criteria, which have been developed to establish the severity of the NEC, are used to diagnose and determine the treatment modality[4]. Today, approximately 20-40% of the patients with NEC are estimated to require surgical intervention, and 50% of these patients have mortality risk[3,5]. In this study, we aimed to evaluate the factors affecting the mortality rate in stage 3b NEC according to modified Bell's classification.

Material and Methods

Between January 2005 and December 2012, patients who were followed up and treated surgically with the diagnosis of stage 3b NEC in our hospital were enrolled in this study. Patients with stage 1 and stage 2 NEC and patients with stage 3b NEC who were operated in another center and subsequently referred to us were excluded from the study.

Initial treatment of all the patients with stage 3b NEC having intestinal perforation was

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primary peritoneal drainage (PPD). Patients were followed closely in the newborn intensive care unit, nasogastric drainage was ensured, broad spectrum antibiotics covering anaerobes were administered, and all the other supportive care was maintained according to the patients' requirements. Following the PPD procedure, if the general condition of the patient improved and the drainage decreased gradually and stopped, no additional surgical procedure was performed; otherwise, laparotomy was done.

Patient records were evaluated retrospectively, and patient demographics, hypoxemia history, major cardiac anomalies, history of oral intake (none, breastfeeding, formula), age at intestinal perforation, drainage content (gas, serofibrinous, stool), operation, laboratory findings (hemoglobin, hematocrit, white blood cell, neutrophil, lymphocyte and thrombocyte counts, coagulation tests, C-reactive protein (CRP), blood urea nitrogen, creatinine, and electrolyte values), positive blood cultures, type of microorganism identified in blood culture, and need for inotropic drug support were investigated in correlation with mortality.

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 15 package software (SPSS Inc.; Chicago, IL, USA). Data were expressed as medians (min-max). Categorical variables were analyzed with the chi-square test or, where appropriate, the Fisher's exact test. Dependent variables were analyzed with the McNemar test, and continuous variables were analyzed with the Mann-Whitney U test. For all the analyses, a *p* value lower than 0.05 was accepted as statistically significant. To define the cut-off point of the variables that were found to be effective on mortality, receiver operating characteristic (ROC) curve analysis was used, and sensitivity, specificity, and positive and negative predictive values were calculated.

Results

Primary peritoneal drainage (PPD) was performed on 31 patients with stage 3b NEC due to intestinal perforation. The gestational ages of the patients varied between 24-40 weeks (median: 32 weeks). Eight (26%) patients needed laparotomy following PPD within 1-10 days (median: 3.4 days). The duration of the follow-up with drain ranged from 1-27 days (median: 3 days). Following treatments, 15 (48%) patients died, while 16 (52%) recovered and were discharged. Following PPD, 5 of the patients died within 24 hours and 8 died within two days. Two of the patients who were treated with PPD required additional drainage procedure through the previous incision because of accidental drain withdrawal, and no additional complications were encountered. Of the patients who required laparotomy, 1 patient was treated with resection and anastomosis and 7 patients were treated with ostomy, and 2 of these patients died within 5-7 days, respectively. Three of the patients' ostomies were closed within 1-1.5 years, and two of the patients' ostomies have not yet been closed. We did not encounter any complications due to laparotomy. In terms of mortality, there was no significant difference between the patients who did and did not require laparotomy. The survival rates were 79% in breastfeeding infants and 39% in infants without enteral feeding, and none of the infants fed with formula survived. The duration of hospitalization ranged from 3-75 days (median: 20 days).

The features of the surviving and exitus patients are summarized in Table I. Gestational age, birth weight, age at NEC diagnosis, major congenital heart diseases, type of drainage, hemoglobin level, hematocrit value, white blood cell count,

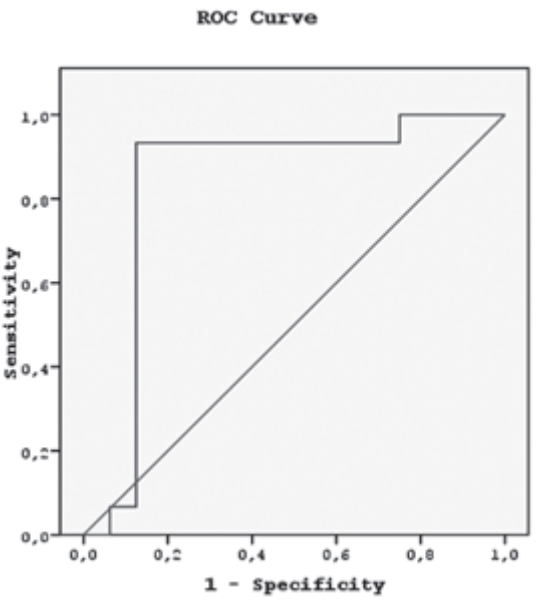

Fig. 1. Receiver operating characteristic (ROC) curve demonstrating the relationship between thrombocytopenia and mortality rate in stage 3b NEC.

neutrophil count, lymphocyte count, CRP level, blood urea nitrogen, and serum electrolyte levels did not have a statistically significant effect on mortality. Low thrombocyte count, high prothrombin time (PT), high activated partial thromboplastin time (aPTT), and high creatinine levels, as well as need for inotropic support were associated with mortality. The mortality risk in stage 3b NEC according to thrombocytopenia was evaluated with ROC analysis, and the cut-off point was found to be 110,000/μL, with 93.3% sensitivity and 87.5% specificity (area under the curve (AUC)=0.838, 95% confidence interval (CI): 0.667-1.008; p=0.001) (Fig. 1). The likelihood ratio was 7.46 and consistency was 90.3%.

Discussion

Necrotizing enterocolitis (NEC) is a multifactorial disease frequently associated with prematurity and low birth weight, whereas it is uncommon in term infants. Intestinal necrosis and perforation are the most serious complications of NEC and are encountered in one-third of the patients[1,3]. Although the mortality related to NEC has decreased due to the new technical innovations of newborn intensive care units in recent years, the disease still carries high mortality rates, up to 20-70%, among the patients requiring surgical intervention[1,3]. The incidence and mortality rate of NEC are inversely proportional with the birth weight and gestational age[3,6]. In this study, we included only the patients with stage 3b NEC having intestinal perforation, but gestational age and birth weight were not correlated significantly with the mortality rate.

Many factors, such as perinatal hypoxemia, asphyxia, congenital heart diseases, polycythemia, and metabolic abnormalities have been blamed in the etiology of NEC[3,7]. Similarly, 81% of our patients had hypoxemia history, and 32% had major cardiac anomalies. Though the effect of congenital cardiac anomalies on the development of NEC is unclear, it is thought to play a significant role in the development of NEC by triggering ischemic changes[3]. Though two of the exitus patients in our study had major congenital heart disease, presence of cardiac disorders did not significantly affect mortality.

Enteral feeding is an important risk factor for development of NEC among preterm infants.

Table I. Evaluation of the Factors Possibly Affecting Mortality Rate in Patients with Stage 3b NEC

	Surviving Patients n=16	Exitus Patients n=15	p value
Gestational age (weeks)	32 (25-40)	29 (24-40)	0.196
Birth weight (g)	1800 (990-3350)	1300 (520-3000)	0.097
Age (days)	7 (1-35)	5 (2-37)	0.498
Gender (M/F)	8/8	9/6	0.722
Hypoxemia	75% (n=12)	87% (n=13)	0.654
Major cardiac anomaly	50% (n=8)	13% (n=2)	0.054
Feeding (none/breastfeeding/formula)	5/11/0	8/3/4	0.01*
Inotropic support	25% (n=4)	100% (n=15)	<0.001*
PPD/PPD+laparotomy	10/6	13/2	0.167
Drainage content (gas/serofibrinous/stool)	4/4/8	0/4/11	0.05
Positive blood culture	25% (n=4)	20% (n=3)	1.000
Hemoglobin (g/dl)	14.9 (8-19)	11.9 (6-18)	0.075
White blood cell count (/mm^3)	9600 (1300-22300)	4800 (1900-39000)	0.692
CRP (mg/L)	35.5 (1-232)	55 (1-119)	0.540
Neutrophil count (/μL)	2130 (230-8300)	1535 (120-5900)	0.324
Lymphocyte count (/μL)	2470 (70-7690)	1800 (1020-7290)	0.696
Blood urea nitrogen (mg/dl)	17 (4-61)	30.5 (9-56)	0.176
Sodium (mEq/L)	134.7 (129-137.8)	134.8 (127.1-150.7)	0.429
Potassium (mEq/L)	4.7 (3.1-6)	4.6 (2.7-6.4)	0.547
Calcium (mEq/L)	8.4 (6.5-9.1)	8.3 (6.3-10.5)	0.963

CRP: C-reactive protein. PPD: Primary peritoneal drainage.

NEC develops following enteral feeding in 90% of the patients[6]. NEC development is encountered less in breastfeeding infants. Many ingredients of breast-milk, such as secretory immunoglobulin (Ig)A, leukocytes, lactoferrin, lysozyme, mucin, cytokines, growth factors, enzymes, oligosaccharides, platelet activating factor (PAF), and polyunsaturated fatty acids have a protective effect against infections and protect the infant from NEC. Recent studies have indicated that breast-milk has an only 50% protective effect against NEC[6,8]. In accordance with the literature, our study demonstrated lower mortality rates in breastfeeding infants.

Neutropenia associated with NEC is considered to be a poor prognostic factor; in case of a granulocyte count <1500/mm^3 at the time of diagnosis, NEC prognosis is estimated to be poor[9,10]. CRP is an acute phase protein and rapidly increases during severe infections or inflammations. A limited number of studies have indicated the significance of CRP increase in the prognosis of NEC[11,12]. Nevertheless, our study demonstrated that the presence of neutropenia and CRP increase were nonspecific markers of the mortality rate in stage 3b NEC.

According to previous reports, thrombocytopenia, disseminated intravascular coagulation and hemolytic anemia are encountered in patients with NEC. Thrombocyte count <150,000/μL is called thrombocytopenia, and thrombocyte count <50000/μL is called severe thrombocytopenia[13]. Ververidis et al.[14] investigated the clinical importance of low thrombocyte level in patients with NEC requiring surgical treatment, and reported that a 100,000/μL thrombocyte level was indicative of intestinal gangrene and a poor prognostic factor, with 69% sensitivity, 60% specificity and 89% positive predictive value. In a recent study of Kenton et al.[15], exitus patients and those requiring laparotomy were found to have lower thrombocyte levels, and they reported that early severe thrombocytopenia may be an indicator of bowel wall necrosis in NEC. Various studies have demonstrated the relationship between NEC and thrombocytopenia[11,14,15], the estimation of bowel gangrene when the thrombocyte count has suddenly and severely decreased[16], and that thrombocyte count following NEC diagnosis might be indicative of the severity of the disease[17]. Thrombocyte count under 100,000/μL is presumed as a poor prognostic factor[14]. In our study, there was a statistically significant relationship between thrombocytopenia and mortality, and the cut-off point for thrombocyte count with ultimate sensitivity and specificity was 110,000/μL. In the circumstance of thrombocyte count under 110,000/μL, the mortality possibility may be estimated to increase 7.46-fold. Therefore, we suggest that the use of 110,000/μL thrombocyte level as the cut-off point with ultimate sensitivity and specificity would be more accurate when evaluating the mortality risk of stage 3b NEC.

Today, the type and timing of surgical treatment remain controversial. Various surgical treatment modalities have been defined for NEC complications, including PPD, resection and anastomosis via laparotomy or laparoscopy, proximal ostomy, multiple ostomies, patch-drain and wait, and clip and leave in the abdominal cavity[3,6,18,19]. For the first time in 1974, Ein et al. [7] suggested performing PPD for NEC perforation, and consequently, they reviewed 13 years' experience with PPD. Their results revealed that performing PPD initially and laparotomy if needed increased the patient survival rate up to 56%. A recent study of Zenciroğlu et al.[1] concerning NEC perforations revealed primary healing in 53% of the patients following PPD procedure without any additional surgical treatments. Many complications may emerge following surgical or medical treatment of NEC. Following surgical procedures, about 20-40% of the patients with NEC are exposed to postoperative complications, such as wound dehiscence, intraabdominal abscess, bowel stricture, intestinal fistula, malabsorption, cholestasis, and short bowel syndrome[20-22]. A recent newborn research report has indicated a 10.3% postoperative intestinal stricture rate, 4.4% wound dehiscence rate and 5.8% intraabdominal abscess rate[22]. During the postoperative course in our study group, no bowel stricture, wound dehiscence, intraabdominal abscess, cholestasis, or intestinal fistula was encountered. Principally, this may be explained by the clearance from the abdominal cavity of infected material by performing PPD. Additionally, improvement in patient status in the initial perforation period might have facilitated the healing period. Moss et al.[23] did not find any significant difference between

peritoneal drainage and laparotomy in terms of survival rate during a 90-day follow-up period. In accordance with the literature, no significant difference was found between the patients with or without surgical intervention after peritoneal drainage in terms of mortality rate.

The limitations of our study were its retrospective patient chart review design and the small number of patients; thus, prospective studies with larger patient series would be much more beneficial.

In conclusion, breastfeeding is significantly effective on survival in patients with stage 3b NEC. Deteriorations in renal (increase in creatinine value), liver (impaired coagulation tests) and cardiac (need for inotropic support) functions are indicators of multiorgan failure leading to mortality. Though there is no available laboratory test estimating the mortality risk of stage 3b NEC alone, we suggest that when the thrombocyte level is 110,000/μL, mortality risk can be estimated more accurately.

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