

# The evaluation of our newborns cases operated due to necrotizing enterocolitis

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## Abstract

**Aim:** This study aimed to investigate the characteristics of newborns operated due to necrotizing enterocolitis (NEC) in newborn intensive care unit and to evaluate the mortality of these patients.

**Material and Methods:** The research was designed retrospectively. The study included 39 patients operated due to NEC in our newborn intensive care unit between January 2010 and December 2015 and their characteristic factors and prognosis were evaluated.

**Results:** The average gestational age and weight at birth of the newborns were 31.5±3.7 weeks, 1861±817 g respectively. There were significant differences between the newborns who died and survived in respect to birth weight, age at the time of operation, presence of antenatal steroid application, hypoxic ischemic encephalopathy, intestinal presence of perforation, blood culture positivity ( $p<0.05$  for all comparisons).

**Conclusion:** NEC is the most common life-threatening gastrointestinal emergency experienced by premature infants cared for in the newborn intensive care unit. It is thought that the most important etiologic factors are prematurity, hypoxia and enteral nutrition. At the same time, it is a devastating gastrointestinal disease that is associated with severe sepsis, intestinal perforation, and significant morbidity and mortality. Its mortality and morbidity rates have been reduced due to developments in newborn intensive care. However, mortality rate is still high among newborns operated due to NEC. For these reasons our thought is that promptly arranged operation time can help to reduce the frequency of mortality.

**Keywords:** Operated Necrotizing Enterocolitis; Mortality; Newborn.

## INTRODUCTION

Necrotizing enterocolitis (NEC) is a disease characterized with partial or complete ischemia of the intestine and most commonly seen in newborn period (1). Although utmost improvements are seen in newborn intensive care unit, but still it continues to be the most important mortality and morbidity in newborn period (2).

Approximately 10% of newborns followed in neonatal intensive care unit can develop NEC. It is mainly observed in premature newborns but 10% of patients with NEC are term newborns (3). Pathophysiology of NEC has not totally been explained but prematurity is main and the most important risk factor. Hypoxia, feeding with nutritional formularies, sepsis, intestinal leukemia and patent ductus arteriosus (PDA) are other risk factors (4).

Abdominal distention, vomiting, gastric residual content, occult or apparent blood in stool, distended and colour-

changes on the abdominal wall, apparent bowel columns, lethargy, apnea and temperature deviations are major clinical findings of NEC. In severe cases, hypotension, respiratory failure and even death can be observed (5).

The treatment of NEC is in the form of medical and surgical treatment. Patients with NEC have high mortality rate and up to 60% mortality rates have been reported especially for the patients requiring surgery. 25-35% of the survivors develop strictures in intestines and it can lead to findings of feeding problems, diarrhea or intestinal obstruction. The most common complications developed in long term are obstruction, fistula, abscess, recurrent NEC, short intestine syndrome, malabsorption, cholestasis and development of enterocystes (6).

In this study, characteristic properties of newborn operated due to NEC in our newborn intensive care unit were evaluated and it was aimed to research the differences between these characteristics in respect to

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survival among the patients with NEC and at the same time to raise awareness on this issue to all physicians.

**MATERIAL and METHODS**

The study was conducted in our newborn intensive care unit among 39 patients operated and followed due to NEC (open surgery) between January 2010 and December 2015. The newborns with major congenital anomalies or gastrointestinal malformations were excluded.

Gender, gestational age, weight, height and head circumference at birth, maternity properties (presence of preeclampsia, chorioamnionitis, early membrane rupture, gestational diabetes), NEC-related diseases [hypoxic ischemic encephalopathy (HIE), respiratory distress syndrome (RDS), PDA] and antenatal steroid application were recorded accordingly (Table 1,2).

**Table1. Demographic Values of newborns operated due to NEC (n:39) Mean±SD (min-max)**

Gender (F/M)	21(53.8%)/18(46.2%)
Gestational age (week)	31.5±3.7(25-40)
Birth weight (g)	1861±817(730-4000)
Birth height (cm)	36.9±3.5(34-50)
Birth head circumference (cm)	26,3±1.9(25-35)

F, Female; M, Male; NEC, Necrotizing Enterocolitis

**Table 2. Distribution of Diseases Affecting NEC in Newborns Operated due to NEC**

HIE	6(15.3%)	
RDS	16(41.0%)	
PDA	6(15.3%)	
Antenatal Steroid Use	12(30.7%)	
Maternal Features	Normal mother	24(61.5%)
	Diabetes	2(5.1%)
	Preeclampsia	7(17.9%)
	Chorioamnionitis /PROM	8(20.5%)

NEC, Necrotizing Enterocolitis; HIE, Hypoxic Ischemic Encephalopathy; RDS, Respiratory Distress Syndrome; PDA, Patent Ductus Arteriosus; PROM, Pre labour Rupture of Membranes

The patients who required surfactant just after the birth were considered as RDS. The patients with a right atrium to aortic root ratio of 1.4 in echocardiographic examination was recorded as PDA. Survival rate, presence of preoperative intestinal perforation, detection time of NEC and the day of operation due to NEC were all recorded for the patients undergone the operation (Table 3).

The diagnosis of NEC was confirmed based on clinical and radiological findings and for this purpose, modified Bell criteria was used (7). Abdominal distention, gastric residual content, vomiting, hematochezia or feeding intolerance were used as presence of clinical findings. Additionally, the presence of these findings were considered as initial stage of NEC. Serial X-ray examinations were performed in every six-hour intervals to the operated patients.

**Table 3. Features of Newborns Operated due to NEC (n:39) Mean±SD (min-max)**

Dead patients	15(38.4%)
Living patient	24(61.5%)
Patients with intestinal perforation	23(58.9%)
NEC start time (day)	10.9±6.4(3-30)
Patients' operating time (day)	19.9±16.4(5-84)

**NEC, Necrotizing Enterocolitis**

The study consisted of very old patients. For this reason, modern methods such as Near-Infrared Spectroscopy (NIRS), ultrasonography/doppler scan, assessment of hepatic blood flow could not be used for NEC's diagnosis. All patients, due to the same reasons, were only given antibiotics and dopamine. No treatment was given to mediators such as tumour necrosis factor (TNF)-alpha.

The statistical difference between the patients with mortality and the patients who survived were searched in respect to demographic values among patients undergone operation due to NEC (Table 4).

**Table 4. The Differences Between Dying and Living in Newborns Operated due to NEC**

	Living Newborns (n:24)(61.5%)	Dying Newborns (n:15)(38.4%)	P değeri
Gender (F/M)	15/9	6/9	0.17
Gestational age (week)	229±25	203±26	0.63
Birth weight (g)	1920±743	1240±854	0.01
Birth height (cm)	37±2.7	34±4.5	0.11
Birth head circumference (cm)	26±1.4	25±2.7	0.21
NEC start time (day)	9±5.5	10±7.1	0.08
Patients' operating time (day)	13±14	29±19	0.04
Patients receiving steroids in the antenatal period	8(20.5%)	4(10.2%)	0.02
Patients with HIE	1(2.5%)	5(12.8%)	0.02
Patients with RDS	7(17.9%)	9(23.0%)	0.06
Patients with PDA	4(10.2%)	2(5.1%)	0.78
Patients with intestinal perforation	7(17.9%)	13(33.3%)	0.02
Patients with positive blood culture	6(15.3%)	11(28.2%)	0.03

F, Female; M, Male; NEC, Necrotizing Enterocolitis; HIE, Hypoxic Ischemic Encephalopathy; RDS, Respiratory Distress Syndrome; PDA, Patent Ductus Arteriosus; PROM, Pre labour Rupture of Membranes

**Statistical analyses**

SPSS 21.0 (SPSS Inc. Chicago, Illinois) was used for statistical analyses. Shapiro-Wilk normality test was utilized to determine whether the data had normal distribution. Data with normal distribution were compared with independent sample t test, and Mann-Whitney U test was used for inter-group comparisons of non-normally

distributed data analysis. Chi-square test was used to analyze categorical variables. Statistical significance was set at  $p < 0.05$ .

## RESULTS

The study included 39 patients operated due to NEC. Of all, 21 patients (53.8%) were female and 18 patients (46.2%) were male. Average gestational age, weight and height at birth were  $31.5 \pm 3.7$  weeks,  $1861 \pm 817$  g and  $36.9 \pm 3.5$  cm respectively (Table 1). Considering all newborns, it was found that there were 5 cases (12.8%) with gestational age of less than 28 weeks and 7 cases (17.9%) with weight at birth of less than 1000 g.

In respect to maternal characteristics, there were 8 mothers (17.9%) with preeclampsia, 8 mothers (20.5%) with prelabour rupture of membranes (PROM), two mothers (5.1%) with gestational diabetes and 24 mothers (61.5%) with normal maternity history (Table 2). The average beginning time for NEC was  $10.9 \pm 6.4$  days and the average age at the time of operation was  $19.9 \pm 16.4$  days. 23 cases had perforation detected before operation. While 61.5% of the patients undergone the operation died, 38.4% of them survived (Table 3).

The first clinical finding was abdominal distention among 24 patients (61.5%), the other first clinical findings were gastric residual content, apnea and vomiting in order. In respect to basal laboratory findings, half of the patients had thrombocytopenia and 9 patients (23%) had leukocytosis while 11 patients (28%) had leukopenia. CRP, an acute phase reactant, was found to have increased in 35 patients (89.7%).

None of the patients developed any important complications such as obstruction, fistula formation or recurrent NEC. Blood culture positivity was found in 13 patients undergone operation (33.3%). The most frequent microorganism was gram negative bacteria found in 11 patients (28.2%). According to blood culture results, bacteria that reproduce in blood culture are *E coli* (n:5), coagulase negative staphylococcus (n:3), *Klebsiella spp* (n:1), *Pseudomonas aeruginosa* (n:2), *Clostridium spp* (n:1), *Candida albicans* (n:4). Blood culture positivity was significantly higher in the patients with mortality (n:11, 28.2%) compared to the patients who survived (n:6, 15.3%) (Table 4).

## DISCUSSION

NEC is the leading gastrointestinal disorder with high morbidity and mortality in newborn period (8). Approximately 10% of newborns followed in neonatal intensive care unit can develop NEC. It is mainly observed in premature newborns (90%) but 10% of patients with NEC are term newborns (9). Mortality varies between 10 to 50% but by the help of latest developments in recent years, mortality rate is reduced to 28% in some centers (10). In this retrospective study, the characteristics of 39 preterm newborns undergone operation for NEC were evaluated.

It was known that the frequency of NEC increase with lower gestational age and lower weight at birth. Wilson et al. evaluated 148 patients with NEC and they found that NEC was observed most frequently among newborns less than 1000 g (42%) (10). Arnold et al. (8) evaluated 128 premature newborns and they found that average gestational age was 32 weeks and average weight at birth was 1466 g. In our study, average birth weight was  $1861 \pm 817$  g. Actually, this value was higher than the previous studies for NEC. The main reason for this result was due to inclusion of patients undergone NEC and patient with other disorders leading to secondary NEC. Low survival rate following operation for NEC among patients with HIE was due to worsening of the prognosis by concomitant presence of HIE and NEC.

In the study, the birth weight of newborns who died were significantly lower compared to the survived newborns (Table 4). This was an expected result considering the nature of the disease and surgical treatment of NEC. Age at time of operation was significantly higher for the newborns who passed away compared to that of survived newborns. It is suggested that delayed intervention may reduce survival rate of the newborns with NEC. Since there is high mortality rate for newborns with perforation, some centers prefer to refer the patient directly to surgery in case of persistent intestinal loops in serial X-rays obtained at 8 to 12-hour intervals, without waiting for deterioration of general status, deep metabolic acidosis, uncorrectable neutropenia or thrombocytopenia (11,12).

We also encouraged this approach and observed that it was proper to refer the patients to surgery before development of perforation if operation was applicable. Consistent with this idea, the decision to operate with conventional techniques may delay the NEC treatment; therefore, current techniques such as bowel ultrasound-doppler, assessment of hepatic blood flow (13), bowel NIRS should be used. The use of these techniques may contribute to the early recognition of the NEC, as a result, the chances of survival for the concerned patients may increase.

Although etiopathogenesis of NEC has not been clarified totally, hypoxia was thought to be the most important triggering factor for development of NEC. As a result of increased intestinal injury due to release of mediators such as TNF-alpha, platelet-activating factor, it is assumed that intestinal ulceration and necrosis occurs. It was known that antenatal steroid application can prevent the release of these mediators and development of NEC. Additionally steroids also increase bile production and reduce bacteria colonization, neutralize endotoxins (14-16). In parallel to these, in our study, the survival rate were higher among the patients to whom antenatal steroid was applied.

There was no significant relation between gender and NEC incidence. In the study involving 20822 NEC patients by Abdulla et al, ratio of males were 54.5% while ratio of females were 45.5% (17). In our study also, 53.8% of

the victims were male while 46.2% of them were female similar to the literature. It is reported that NEC develops most frequently in the second week of the life. Stoll et al. reported the detection time of the disease as 20.2 days in their study (18). Thus, it was advised to feed premature and very low birth weight newborns with small amount in following few days postnatally known as early trophic feeding and it is shown that early trophic feeding has no negative effect on NEC development (19). In our study, we found that beginning time for NEC was  $10.9 \pm 6.4$  days. This difference was attributed to different feeding attitudes and other predisposing factors frequently found in these cases.

It has been reported that 10-30% of the patients with NEC has positive culture result primarily for gram negative bacteria in blood or eritoneal fluid. Although the responsible bacteria can vary according to the center in concern, the most frequently seen agents are E coli, Klebsiella spp, Pseudomonas aeruginosa, Enterobacter spp, coagulase negative staphilococcus, Clostridium spp. and Candida albicans (6). In our study, 17 patients (43.5%) showed blood culture positivity. Blood culture positivity was significantly higher in the patient with higher mortality compared to the patients who survived. Additionally, similar to blood culture positivity, perforation was higher in the patient with higher mortality compared to the patients who survived.

Although mortality due to NEC varies between 10 to 50%, there have been some centers reporting that mortality rate was reduced to 28 to 30% by the help of early diagnosis, close follow-up and prompt treatment (8). Mortality rate in our study was found to be substantially higher compared to the literature. The reason of this result was due to the inclusion of the patients with stage-3 NEC.

The important complication of patients with operated NEC was feeding problems in short term and 12 patients (30.7%) developed this complaint. In long term, malabsorbtion was the most frequent complication (23%). Following surgical or medical treatment, it was reported that the survivors develops intestinal obstructions with a rate of 25 to 35%. It was suggested that obstructions/strictures develop at non-perforated bowel segment due to scarring. Most probably they are symptomatic in acute stage but sometimes, some obstructions can be asymptomatic as long as to 6 months following the event. These patients can reveal feeding problems, diarrhea or bowel obstruction (20).

However, none of our patients revealed obstruction both in short and long term. Delay or interruption in enteral feeding can lead to inhibition of hormonal secretion and impairment of gastrointestinal adaptation among newborns with very low birth weight (21,22). Feeding problems in our patients can be explained by this mechanism considering the absence of anatomical disorders. This result supports the hypothesis that gastrointestinal inhibition develops due to long-lasting

period of treatment for patients with stage-3 NEC, more delayed installation of enteral nutrition.

## REFERENCES

1. Lee JS, Polin RA. Treatment and prevention of necrotizing enteocolitis. *Semin Neonatol* 2003;8(6):449-59.
2. Fell JM. Neonatal inflammatory intestinal diseases: necrotizing enterocolitis and allergic colitis. *Early Hum Dev* 2005;81(1):117-22.
3. Henry MC, Moss RL. Current issues in the management of necrotizing enterocolitis. *Semin Perinatal* 2004;28:221-33.
4. Hsueh W, Caplan MS, Qu XW, Tan XD, De Plaen IG, Gonzalez-Crussi F. Neonatal necrotizing enterocolitis: clinical considerations and pathogenetic concepts. *Pediatr Dev Pathol* 2003;6(1):6-23.
5. Ragazzi S, Pierro A, Peters M, Fasoli L, Eaton S. Early full blood count and severity of disease in neonates with necrotizing enterocolitis. *Pediatr Surg Int* 2003;19(5):376-9.
6. Dimmit RA, Lawrance R. Clinical management of necrotizing enterocolitis. *American Academy of Pediatrics* 2001;2:110-7.
7. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am* 1986;33(1):179-201.
8. Arnold M, Moore SW, Sidler D, Kirsten GF. Long-term outcome of surgically managed necrotizing enterocolitis in a developing country. *Pediatr Surg Int* 2010;26:355-60.
9. Kaul A, Balisteri WF. Necrotizing enterocolitis. In: Fanaroff AA, Martin RJ (eds). *Neonatal Perinatal Medicine: Diseases of the fetus and infant*. 7nd edition. St. Lois: Mosby; 2002. p.1299-307.
10. Wilson R, Kanto WP Jr, McCarthy BJ, Burton T, Lewin P, Terry J et al. Epidemiologic characteristics of necrotizing enterocolitis: apopulation-based study. *Am J Epidemiol* 1981;114(6):880-7.
11. Cass DL, Wesson DE. Advances in fetal and neonatal surgery for gastrointestinal anomalies and disease. *Clin Perinatol* 2002;29(1):1-21.
12. Butter A, Flageole H, Laberge JM. The changing face of surgical indications for necrotizing enterocolitis. *J Pediatr Surg* 2002;37(3):496-9.
13. Akin MA, Yikilmaz A, Gunes T, Sarici D, Korkmaz L, Ozturk MA, et al. Quantitative assessment of hepatic blood flow in the diagnosis and management of necrotizing enterocolitis. *J Matern Fetal Neonatal Med*. 2015;28(18):2160-5.
14. Ng PC, Li K, Wong RP, Chui K, Wong E, Li G, et al. Proinflammatory and anti-inflammatory cytokine responses in preterm infants with systemic infections. *Arch Dis Child Fetal Neonatal Ed* 2003;88(3):209-13.
15. Sehdev HM, Abbasi S, Robertson P, Fisher L, Marchiano DA, Gerdes JS, et al. The effects of the time interval from antenatal corticosteroid exposure to delivery on neonatal outcome of very low birth weight infants. *Am J Obstet Gynecol* 2004;191(4):1409-13.
16. Claud EC, Walker WA. Hypothesis: inappropriate colonization of the premature intestine can cause neonatal necrotizing enterocolitis. *Faseb J* 2001;15(8):1398-403.
17. Abdullah F, Zhang Y, Camp M, Mukherjee D, Gabre-Kidan A, Colombani PM, et al. Necrotizing Enterocolitis in 20 822 Infants: Analysis of Medical and Surgical Treatments. *Clin Pediatr (Phila)* 2010;49(2):166-71.
18. Stoll BJ, Kanto WP Jr, Glass RI, Nahmias AJ, Brann AW Jr. Epidemiology of necrotizing enterocolitis: a case control study. *J Pediatr* 1980;96(3 Pt):447-51.

19. Bombell S, McGuire W. Early trophic feeding for very low birth weight infants. *Cochrane Database Syst Rev* 2009;8(3):CD000504.
20. Coombs RC. The prevention and management of necrotizing enterocolitis. *Current Paediatrics* 2003;13(3):184-9.
21. Filidl-Rimon O, Branski D, Shinwell ES. The fear of necrotizing enterocolitis versus achieving optimal growth in preterm infants- an opinion. *Acta Paediatr* 2006;95(11):1341-4.
22. Hällström M, Koivisto AM, Janas M, Tammela O. Laboratory parameters predictive of developing necrotizing enterocolitis in infants born before 33 weeks of gestation. *J Pediatr Surg* 2006;41(4):792-8.