



### Comparison of Risk Factors in Necrotizing Enterocolitis among Infants in Neonatal Intensive Care Unit

Yenidoğan Yoğun Bakım Ünitesindeki Bebeklerin Nekrotize Enterokolit Risk Faktörlerinin Karşılaştırılması

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#### ABSTRACT

**Purpose:** Necrotizing enterocolitis is one of the important problems of premature infants. The incidence is about 1-5% in infants followed in neonatal care units and inversely related to gestational age and birth weight.

**Materials and Methods:** In this study, 31 infants with necrotizing enterocolitis and 31 infants with similar gestational age and birth weight as control group hospitalized in Cukurova University Neonatal Care Unit between 1 January 2001-31 January 2004 were evaluated.

**Results:** The incidence of necrotizing enterocolitis in this period was 1.4 (31/2214 admission). Mean gestational age was  $30.5 \pm 3.2$  weeks (25-36), mean birth weight was  $1331 \pm 384$  (730-2150) grams while 71% was younger than 32 gestational weeks and 67.7% was under 1500 grams. The signs of NEC were detected at a mean of  $11.2 \pm 10$ . (2-38) days. Twenty-six (83.9%) were being fed at the time of the necrotizing enterocolitis signs appeared. According to the Walsh and Kliegman classification, 19 (61.3%) infants were in stage 1 (17 were 1a, 2 were 1b); 3 (9.6%) infants were in stage 2a, 9 (%29.1) infants were in stage 3 (7 were in 3b). Blood culture was positive in 7 (%22.6) infants with predominance of gram negative microorganisms (5 infants). Eleven (%35.5) infants were exitus, 12 were discharged. Hypoxia, respiratory distress syndrome, intraventricular hemorrhage and umbilical catheterization were significant risk factors in necrotizing enterocolitis. Thrombocytopenia, leucopenia and high C-reactive protein levels were significantly high in necrotizing enterocolitis group. Breast feeding is significantly high in control group.

**Conclusion:** Necrotizing enterocolitis, is a leading cause of morbidity and mortality in neonatal intensive care units. Early breast feeding with small amounts, increasing amount of milk slowly, antenatal steroids, caring hygiene rules can prevent the development of it.

**Key Words:** Neonate, Necrotising enterocolitis, risk factors

#### ÖZET

**Amaç:** Nekrotize enterokolit prematüre bebeklerde rastlanan en önemli problemlerden biridir. Yenidoğan bakım ünitesindeki bebeklerin %1-5'inde görülmekte olup gebelik yaşı ve doğum ağırlığı ile ters orantılıdır.

**Materyal ve Metod:** Bu çalışmada Çukurova Üniversitesi Yenidoğan Bakım Ünitesinde 1 Ocak 2001- 31 Ocak 2004 yılları arasında nekrotize enterokolit tanısı konan 31 bebek ile aynı gebelik yaşı ve doğum ağırlığına sahip kontrol grubu karşılaştırmalı olarak değerlendirilmiştir.

**Bulgular:** Bu dönemdeki nekrotize enterokolit görülme sıklığı 1,4 (31/ 2214 kabul edilen hasta) olarak belirlenmiştir. Ortalama gebelik yaşı  $30,5 \pm 3,2$  hafta (25-36), Ortalama doğum ağırlığı  $1331 \pm 384$  (730-2150) gramken %71'i 32 gebelik haftasından erken ve %67,7'si 1500 gr'ın altında idi. NEC semptomlarının saptanama süresi ortalama  $11,2 \pm 10$  (2-38) gündür. Bebeklerin 26'sı (%83,9) nekrotize enterokolit belirtileri ortaya çıktığında düzenli olarak besleniyorlardı.

beslenme sırasında NEC'e rastlanmıştır. Walsh ve Kliegman sınıflandırmasına göre; bebeklerin 19'u 1. Evrede (17'si 1a, ikisi 1b), Üçü 2a evresinde, dokuzu üçüncü evrede (Yedisi 3b) sınıflandırılmıştır. Kan kültürünün 7 (%22.6) bebekte pozitif çıktığı ve bunların beşinde gram negatif mikroorganizmalar olduğu tespit edilmiştir. Bebeklerin onbirinde (%35.5) ölüm gerçekleştiği, 12'sinde taburcu olduğu saptanmıştır. Hipoksi, respiratuar distres sendromu, intraventrikuler kanama ve umbilikal katater uygulaması nekrotize enterokolitteki önemli risk faktörleridir. Trombositopeni, lökopeni, ve C-reaktif proteinindeki artış nekrotize enterokolitli grupta oldukça yükselmiştir. Emzirme kontrol grubunda oldukça yüksektir.

**Sonuç:** Nekrotize enterokolit yenidoğan bakım ünitelerinde en sık hastalık ve ölüme yolaçan nedenlerden biridir. Az miktarlarda erken emzirme, sütün yavaşça miktarının artırılması, antenatal steroidler ve hijyen kurallarının önemszenmesiyle bu hastalığın gelişiminin önüne geçilebilir.

**Anahtar Kelimeler:** yenidoğan, nekrotize enterokolit, risk faktörleri.

## INTRODUCTION

Necrotizing enterocolitis (NEC) is one of the important problems of premature infants. Although several predisposing factors have been identified such as prematurity, enteral feeding and infection, its pathogenesis remains elusive. Advances in the supportive care of premature babies, such as use of surfactant, improved technologies for mechanical ventilation and wider availability of skilled personnel enable the very premature to survive, and in so doing increase in population of patients susceptible to NEC. The incidence is about 1-5 % in infants followed in neonatal care units and inversely related to gestational age and birth weight<sup>1</sup>. The purpose of this retrospective study is to evaluate perinatal and neonatal risk factors of occurrence of NEC in Neonatal Intensive Care Unit.

## MATERIAL AND METHODS

The medical records of 31 newborn infants who developed NEC as a study group and 31 newborns that did not develop NEC as a control group admitted to the Neonatal Intensive Care Unit (NICU), Çukurova University Faculty of Medicine, between 1 January 2001-31 January 2004 were reviewed. Data pertaining to maternal history, ante partum events, gestational age, birth weight, gender, Apgar scores, premature prolonged membrane rupture, presence of mechanical ventilation therapy, existence of hypothermia, hypotension and hypoxia, RDS, surfactant therapy,

polycythemia or anemia, PDA and indomethasine treatment thrombocytopenia or thrombocytosis, leucopenia, exchange transfusion, congenital gastrointestinal anomaly, cyanotic congenital heart defects, intraventricular hemorrhage, umbilical catheterization, feeding schedules, time of diagnose and first symptoms of the NEC, time of the feeding, C-reactive proteins, NEC staging, radiological findings, blood culture, antibiotics used for NEC treatment and outcomes of patients were collected retrospectively.

Necrotizing Enterocolitis was diagnosed and staged according to modified Bell's classification<sup>2</sup>.

The study was approved by the Ethical Committee of the University. We obtained informed consent from the parents/guardians of all participants involved in our study.

**Statistical analysis:** Data was analysed using the SPSS-X 11 for Windows. Results are given as mean  $\pm$  standard deviation.

## RESULTS

The incidence of necrotizing enterocolitis in this period was 1.4 % (31/2214admission). 31 infants with NEC (group N) were compared with 31 controls without NEC (group C). In group N, mean gestational age was  $30.5 \pm 3.2$  weeks (25-36), mean birth weight was  $1331 \pm 384$  (730-2150) grams while 71% was younger than 32 gestational weeks and 67.7% was under 1500 grams. The signs of NEC were detected at a mean of  $11.2 \pm$

10. (2-38 days. Twenty-six (83.9%) infants were being fed at the time of the NEC signs appeared. According to the Walsh and Kliegman classification, 19 (61.3%) infants were in stage 1 (17 were 1a, 2 were 1b); 3 (9.6%) infants were in stage 2a, 9 (%29.1) infants were in stage 3 (7 were in 3b). Blood culture was positive in 7 (%22.6)

infants with predominance of gram negative microorganism (5 infants). Eleven (%35.5) infants were exitus, 12 were discharged. Eight patients in stage 1 were sent to other hospitals. The characteristics of the patients were shown in Table 1 and 2.

**Table 1. Properties of study group with Necrotizing Enterocolitis**

Birth weight	1331 ± 384 (730-2150) gram
Gestational age	30.5 ± 3.2 weeks (25-36)
Apgar scores	1.min 5.2 ± 2.1 (1-9) 5.min 7.2 ± 1.8 (3-10)
First feeding started at	5.4 ± 3.95 (2-18) days
Number of enterel feeding babies at the time of diagnosis	26 (83.9%)
Mean postnatal days of onset of NEC symptoms	11.2 ± 10. (2-38)
Symptoms and signs	Abdominal distention (55.1%) Bilious vomiting (15%) Apnea (12%) Non-bilious vomiting( 6%)
Staging according to Walsh and Kliegman	20 (61.3%) stage 1 2 (6.5%) stage 2 9 (29.1%) stage 3
Radiological findings	Nonspecific findings: 15 (48.4%) pneumotosis intestinalis: 2 (6.5%) Symptoms of ileus: 2 (6.5%) sentinel loop: 2 (6.5%) perforation: 6 (19.4%)
Blood culture (+)	7 (22.6%)
Prognosis	Cure 12 (38.7%) Exitus 11 (35.5%) To another hospital (8 patients at stage 1)

**Table 2.: Comparision of study and control group**

	Group N	Group C	p
Mean gestational age	30,4 ± 3	31,3 ± 2	<0.05
Mean birth weight	1330 ± 384	1440 ± 353	<0.05
Apgar at 1 <sup>st</sup> minute	5 ± 2	5,5 ± 1,5	<0.05
Apgar at 5 <sup>th</sup> minute	7 ± 1,8	7,5 ± 1,2	<0.05
CRP	<b>20 ± 2,2</b>	<b>4,5 ± 6,8</b>	<b>&gt;0.05</b>

CRP: C-reactive protein

**Table 3: Analysis of risk factors of study group and control group**

RISK FACTORS	Group N	Group C	p
UMR	7/31	4/31	>0.05
EMR	9/31	7/31	>0.05
Sex M/F	16/15	21/10	>0.05
Hypothermia	6/22	5/25	>0.05
Hypoxia	8/22	2/30	<0.05

RDS	17/31	5/31	<0.05
Hypotension	3/23	-	>0.05
Surfactant Therapy	5/30	2/31	>0.05
Ventilator Therapy	22/31	15/31	>0.05
Indomethacine treated-PDA	4/30	2/31	>0.05
Anemia	10/28	8/31	>0.05
Polycythemia	2/24	1/31	>0.05
Thrombocytopenia	13/27	8/31	>0,05
Leucopenia	10/24	1/31	<0.001
IVH	15/26	8/31	<0,05
Umbilical catheterization	8/22	3/30	<0,05
Feeding breast milk/formula or mix	4/17	20/27	<0,001

UMR: prolonged membrane rupture, EMR: early membrane rupture, M/F: male/female, RDS: respiratory distress syndrome, PDA: patent ductus arteriosus, IVH: intraventricular hemorrhage

## DISCUSSION

Neonatal necrotizing enterocolitis remains the most common gastrointestinal emergency encountered in the newborn intensive care units. It affects approximately 11% of the premature neonates weighing less than 1500 gram<sup>3</sup>. Despite medical advances that would potentially reduce the incidence of the disease, the incidence of NEC remains unchanged over the last 20 years<sup>4,5</sup>. In our study the incidence of NEC in the study period is 1.4% in Neonatal Intensive Care Unit.

Etiology of NEC is multifactorial and the most important risk factors are prematurity, hypoxia and/or intestinal ischemia and enteral feeding, gastrointestinal bacteria colonization. At least 80% of the patients are preterm or have low or very low birth weight, and the incidence of the disease is inversely proportional to the gestational age<sup>6,7,8</sup>. In this study most of the patients were premature with a mean gestational age of  $30.5 \pm 3.2$  weeks (25-36) and birth weight was  $1331 \pm 384$  (730-2150) gram.

Despite significant research and the extensive morbidity and mortality associated with the disease, its pathogenesis remains largely unknown. Necrotizing enterocolitis has multifactorial etiology. Mainly hypoxia and RDS were the significant risk factors in developing NEC ( $p < 0.05$ ) in group N. Although Apgar scores at 1<sup>st</sup>

and 5<sup>th</sup> minute did not differ between groups, in the following period, hypoxia may occur. In premature infants hypoxia may result from pulmonary immaturity or overwhelming sepsis with pronounced hypotension. Episodic hypoxia may lead to intestinal blood flow decrease through a mechanism similar to the diving aquatic animals<sup>9</sup>. Prenatal administration of corticosteroids, promoting maturation of gastrointestinal mucosal barriers as well as surfactant synthesis to prevent RDS can influence NEC progression. We would like to point out that we have not evaluated the antenatal steroid administration because of limited information.

We could not find significant relation between PPRM and NEC. Hypothermia and hypotension also were not related with NEC.

Although the association between indomethacine-treated PDA and NEC is debated, the use of indomethacine for medical closure of PDA may compromise intestinal blood flow. We did not find any relation between PDA and NEC in control group and NEC group.

The development of NEC occurs more frequently in infants fed with formula than those fed with breast milk<sup>10</sup>. Enteral feeding and the pattern of intestinal colonization and bacteria adherence are risk factors for developing NEC<sup>3</sup>. Breast

feeding influences the developing enteric flora of newborn infants. Breast feeding causes gastrointestinal colonization predominantly by bifidobacterium, in contrast, formula fed neonates colonize predominantly by coliforms, enterococci and bacteroides<sup>11</sup>. In our study feeding with breast milk seem to be a protective factor for NEC. In NEC group more infants were fed with formula or formula plus breast milk ( $p < 0.001$ ). In NEC group %83.9 babies were feeding at the time of diagnosis.

Intestinal ischemia and hypoxia in premature infants may result from umbilical artery catheterization with possible clot formation<sup>12,13</sup>. In our study umbilical catheterization was significantly higher in NEC group ( $p < 0.05$ ).

Certain bacterial species have been associated with outbreaks of NEC, but most species are endemic to nicus and may represent the gastrointestinal colonization species of most premature infants<sup>14,15</sup>. Within the last few decades various NEC epidemics have been reported in the literature<sup>12</sup>. There are studies suggesting that coagulase negative staphylococci are commonly involved in NEC and are associated with high rates of mortality and morbidity<sup>16,17</sup>. In one of the epidemic reports, the authors suggested a synergism exist between rotavirus and klebsiella, resulting in an increased pathogenesis<sup>18</sup>. In our study mostly gram negative microorganisms were isolated in blood cultures.

Because the underlying clinical circumstances are not uniform, NEC may present a syndrome with common findings and variety of etiologies. Necrotizing enterocolitis begins at 10-15 days after birth in preterm infants where as 2-3 days in term infants. Onset of NEC symptoms in this study was evident at  $11.2 \pm 10$  postnatal days. In any case, the clinical consequences do not differ substantially in various patient populations, including the infants of extremely low birth weight or extreme maturity<sup>19</sup>.

Early symptoms of NEC are indistinguishable from sepsis neonatarum. The signs and symptoms

are quite variable, ranging from feeding intolerance to evidence of a fulminate intraabdominal catastrophe. Usually the infant manifests abdominal distention, vomiting, increased gastric residual, lethargy, apnea, bradycardia or guiac positive stool<sup>13</sup>. In our study, abdominal distention (%55.1) was the predominant symptom in NEC.

Radiological evaluation for an infant with suspected NEC should include a flat plate radiograph of the abdomen with either a left lateral decubitis or cross table lateral radiograph to evaluate bowel perforation. Pneumotosis intestinalis represents the accumulation of hydrogen, carbon dioxide and methane gas, products of bacterial fermentation in the subserosal and sub mucosal layers of gastrointestinal wall<sup>13</sup>. In our study radiological evaluation yields mostly nonspecific findings. Although pneumotosis intestinalis has been detected in a small number of babies (%6.5), pneumoperitoneum has been detected in % 19.4 infants.

The laboratory evaluation of such infants often demonstrates neutropenia, elevation of acute phase reactant, C reactive protein<sup>13</sup>. a consumptive thrombocytopenia associated with disseminated intravascular coagulability also may be evident. Thrombocytopenia, anemia or polycytomia were not significantly different between groups, but leucopenia found to be significantly related with NEC ( $p < 0.001$ ) and also C reactive protein was significantly higher in NEC group (Table 2). Although our study is limited by its retrospection, it has allowed us to analyze risk factors in NEC development.

Treatment of NEC begins with prompt recognition of the diagnosis. All enteral feeding and medication should be discontinued and decompression of gastrointestinal system with gastric tube placement has to be performed to evacuate both residual air and fluid. For infants with proven NEC, surgical intervention is indicated in approximately 50% of cases. The most common sequel of NEC is bowel stricture formation and

short gut syndrome. In this study 6 of the patients needed surgical operation.

In conclusion, prevention of NEC still remains elusive. Avoidance of premature birth, use of antenatal steroids, frequent breast feeding seem to be a reasonable strategy to reduce the incidence of NEC.

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