ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Retrospective Analysis of Surgical Treatment of Stricture Following Necrotizing Enterocolitis

Nekrotizan Enterokolit Sonrası Striktürlerin Cerrahi Tedavisinin Retrospektif Analizi

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Abstract

Introduction: Necrotizing enterocolitis (NEC) is a severe gastrointestinal problem that predominantly affects premature babies. The aim of this retrospective study was to evaluate patients who underwent surgical treatment for NEC and newborns who initially recovered with medical treatment but later developed a stricture and required surgery.

Materials and Methods: We analyzed patients diagnosed with NEC between January 2009 and December 2021. Our study included patients who developed strictures after initially receiving medical treatment for NEC and subsequently underwent surgery. Demographic findings, mother's age, gestational weeks, birth weight, type of birth, postnatal age at NEC diagnosis, pH, first C-reactive protein (CRP) after onset of symptoms, leukocytes, hemoglobin and thrombocytes at the onset of NEC, echocardiography results, age at surgery, blood values before surgery, surgery technique, and outcomes were retrospectively analyzed.

Results: Out of 40 patients who underwent primary surgery for NEC during the newborn period, 6 patients underwent surgery after initially receiving medical treatment. The female-to-male ratio was 15/31, and the median gestational age was 29 weeks. The median mother's age was 30 years, and the median birth weight was 1097g. The median postnatal age at NEC onset was 6 days (range 2-39). Echocardiography was performed in 43 patients, with 6 showing normal results and 28 having congenital cardiac anomalies. The median surgery day for patients who underwent primary surgery for NEC was 19 days (range 2-90). Ileostomy was performed in 26 patients, colostomy in 8 patients, and ileostomy plus colostomy in 1 patient. Surgery was conducted in 6 out of 392 patients who developed post-NEC strictures after initial medical treatment. Comparison between post-NEC stricture patients and those who underwent surgery for NEC revealed significant differences only in the age at surgery (p=0.024).

Conclusion: Patients who clinically experience NEC should be considered for the development of strictures, especially in cases of prolonged feeding intolerance, distention, gastric residual, and rectal bleeding. Therefore, close follow-up and multidisciplinary approaches are crucial, and contrast barium radiography should be the initial diagnostic step.

Keywords
Necrotizing enterocolitis, stricture, surgery

Anahtar kelimeler
Nekrotizan enterokolit, striktür, cerrahi

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Öz

Giriş: Nekrotizan enterokolit (NEK), çoğunlukla prematüre bebekleri etkileyen ciddi bir gastrointestinal sorundur. NEK nedeniyle cerrahi tedavi yapılan hastalar ile medikal tedavi ile iyileşen ve sonrasında striktür gelişip cerrahi yapılan yenidoğan hastalarını retrospektif olarak değerlendirmeyi amaçladık.

Gereç ve Yöntem: Ocak 2009 ile Aralık 2021 tarihleri arasında NEK tanısı alan hastaları inceledik. Çalışmamıza cerrahi yapılan ve medikal olarak tedavi edildikten sonra striktür gelişen ve ameliyat edilen hastalar dahil edildi. Demografik bulgular, anne yaşı, doğum haftası, doğum ağırlığı, doğum şekli, NEK tanısının doğum sonrası yaşı, pH, semptomların başlangıcından sonraki ilk C-reaktif Protein (CRP), NEK başlangıcındaki lökosit, hemoglobin ve trombositler, ekokardiyografi, ameliyat yaşı, ameliyat öncesi kan değerlerinin aynı olması ameliyat tekniği ve sonuçları retrospektif olarak incelendi.

Bulgular: Yenidoğan döneminde 40 hastaya NEK nedeniyle primer cerrahi uygulandı, 6 hastaya ise medikal tedavi sonrası cerrahi uygulandı. Hastaların kadın/erkek oranı 15/31 olup, ortalama gebelik yaşı 29,5 hafta idi. Hastalarımızın ortanca anne yaşı 30,0 yıl ve ortanca doğum ağırlığı 1097 g idi. NEK başlangıcında ortalama doğum sonrası yaş 6 gündü (2-39 aralığı). Toplam 43 hastaya ekokardiyografi yapılabildi ve bunların 6'sı normal, 28'inde konjenital kalp anomalisi vardı. NEK nedeniyle primer cerrahi uygulanan hastaların ortanca ameliyat günü 19 gün (dağılım 2-90) idi. 26 hastaya ileostomi, 8 hastaya kolostomi, 1 hastaya ileostomi artı kolostomi yapmak zorunda kaldık. NEK için tıbbi tedavi sonrasında NEK sonrası darlık gelişen 392 hastanın 6'sına cerrahi uygulandı. NEK sonrası darlık geçiren hastaları NEK nedeniyle ameliyat edilen hastalarla karşılaştırdığımızda sadece ameliyat yaşında anlamlı sonuçlar elde ettik (p=0,024).

Sonuç: Klinik olarak NEK geçirmiş hastalarda, uzun süreli beslenme intoleransı, şişkinlik, mide rezidü ve hatta rektal kanaması olan hastalarda NEK sonrası gelişen darlıklar mutlaka göz önünde bulundurulmalıdır. Bu nedenle yakın takip ve multidisipliner yaklaşımlar çok önemlidir ve tanı için öncelikle kontrast baryumlu radyografi yapılmalıdır.

Introduction

Necrotizing enterocolitis (NEC) stands as the most prevalent gastrointestinal disease necessitating surgical intervention during the neonatal period, primarily affecting premature and low birth weight infants. There are many published studies in the literature on the etiopathogenesis, classification or treatment of NEC disease. Another problem that may cause serious morbidity in newborns with NEC is the stricture that may occur after the acute period of NEC almost seen 1/3 of the patients (1).

Strictures may manifest in NEC patients, whether treated medically or surgically. Limited research on this matter suggests a lower incidence of stricture development post-medical treatment compared to surgical intervention (2). The critical period for stricture occurrence spans the initial three months after an acute NEC episode, potentially leading to severe complications such as obstruction, perforation, sepsis, and even mortality in infants (1, 2).

In neonates who resume full nutrition post-acute NEC but remain hospitalized in neonatal intensive care due to additional ailments or pronounced prematurity, the emergence of distension should prompt consideration of stricture development following NEC.

While pre-surgery diagnosis poses challenges, contrast-enhanced passage films can prove beneficial. It is imperative to be mindful that patients who underwent surgery and received an ostomy for NEC, particularly those with necrosis and perforation, may develop strictures in the distal part of the ostomy.

The purpose of our study is to evaluate neonatal patients who have had necrotizing enterocolitis recovered with medical therapy and developed strictures that require surgical intervention retrospectively.

Materials and Methods

We conducted a retrospective analysis of patients diagnosed with NEC at the Neonatal Intensive Care Unit in Karadeniz Technical University Faculty of Medicine between January 2009 and December 2021. Ethical approval for data collection review was obtained from the local ethical committee (date: 06.01.2020 approval number: 2019-337). Our study included patients who developed strictures following medically treated NEC and subsequently underwent surgery. Various parameters, including gender, age, maternal age, gestational weeks, birth weight, type of birth, postnatal age at NEC diagnosis, pH at NEC onset, initial C-reactive protein (CRP) CRP levels after symptom onset, leukocyte count, hemoglobin, thrombocyte levels at NEC onset, echocardiography results, age at surgery, identical blood values before surgery, surgery technique, and outcomes were retrospectively evaluated.

Statistical Analysis

Categorical variables were presented as percentages, and numeric variables were expressed as median (minimum - maximum) values. Fisher's Exact test was employed for comparing categorical variables, while the Mann-Whitney U test was used for non-normally distributed numerical variables. Missing data for patient information were substituted with the median of available data. A two-way p-value <0.05 indicated statistical significance.

Results

Between June 2009 and December 2021, 561 patients diagnosed with NEC. 114 patients died during the NEC treatment at the newborn period. 55 patients required surgery and 392 patients responded to medical treatment of NEC from the total of 447 (79%) surviving patients. 40 patients done primary surgery for NEC at the newborn period whom did not respond to medical treatment, 6 patients done surgery after medically treated NEC patients due to stricture after medical treatment and there were a total of 9 missing values. Flow diagram of the study selection is shown in Figure 1. Female/Male F/M ratio of patients was 15/31 and the patients median gestational age was 29 weeks. The median mother age of our patients was 30 years and median birth weight was 1097 g (range 490-4160). A total of 42 patients (91%) were born with cesarean section (C/S). The median postnatal age at NEC onset was 6 days (range 2-39). The pH at onset of NEC, first CRP after onset symptoms, leukocytes, hemoglobin and thrombocytes at onset of NEC values are shown in Table 1. Echocardiography could be performed in a total of 43 patients and 6 of them were normal, 28 of them atrio septal defect (ASD), patent ductus arteriosus (PDA), and patent foramen ovale PFO and 9 of them tetralogy of fallot, mitral regurgitation (MR), tricuspid regurgitation (TR) and ventricular septal defect (VSD).

The median surgery day of patients who underwent primary surgery for NEC was 19 days (range 2-90). We had to perform ileostomy in 26 patients, colostomy in 8 patients, and ileostomy plus colostomy in 1 patient. Perioperative findings of the patients included ileum necrosis in 2 patients, colonic necrosis in 1 patient, ileal perforation in 5 patients and colonic perforation in 3 patients. The preoperative median CRP, leukocytes, hemoglobin and thrombocytes values of the patients are presented in the Table 1.

Surgery was performed in 6 of 392 patients who had post-NEC strictures occured after medically treated for NEC. Post-NEC strictures were mainly located in descending colon, sigmoid and ileum. Radiopaque film of the patient with stricture after medical treatment of NEC in the sigmoid colon is shown in Figure 2.

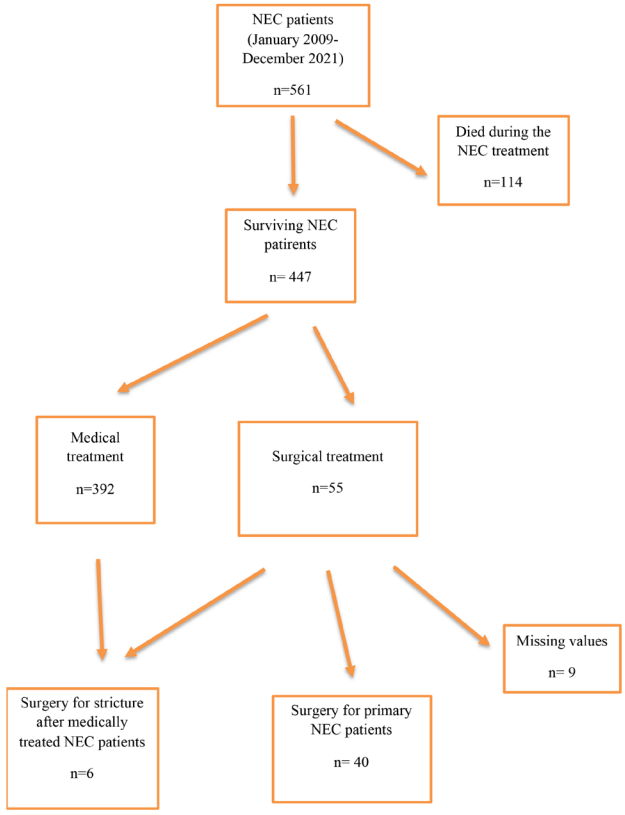


Figure 1. Flow diagram of the study selection



Figure 2. Radiopaque film of the patient with stricture after medical treatment of NEC in the sigmoid colon (area marked with red arrow)

Table 1. Demographic features of our study (n=46)		
Characteristics		**Median (min-max)**
Male*		31 (67%)
Gestational age (week)		29 (23-40)
Mother age (year)		30 (20-45)
Birth weight (g)		1097 (490-4160)
Type of birth (C/S)*		42 (91%)
PNA at NEC diagnosis, days		6 (2-39)
pH at onset of NEC		7.30 (7.02-7.40)
First CRP after onset symptoms (mg/L)		3 (0-150)
Leukocytes at onset of NEC (10^9/L)		8 (1-15)
Hemoglobin at onset of NEC (mmol/L)		13 (6-18)
Thrombocytes at onset of NEC (10^9/L)		185 (50-409)
Echocardiography (n=43)*	Normal ASD-PDA-PFO Tetralogy of fallot-MR-TR-VSD	6 (14%) 28 (65%) 9 (20%)
Surgery age (day)		19 (2-90)
Surgery technique*	Ileostomy Colostomy Ileal nekrosis Colonic nekrosis Ileal perforation Colonic perforation Ileostomy + Colostomy	26 (56%) 8 (17%) 2 (4%) 1 (2%) 5 (10%) 3 (6%) 1 (2%)
CRP before surgery (mg/L)		3 (0.2-105)
Leukocyte before surgery (10^9/L)		7 (1-20)
Hemoglobin before surgery (mmol/L)		11 (8-17)
Thrombocytes before surgery (10^9/L)		190 (11-650)
Post NEC stricture	Ileum (1) Colon (descending colon, sigmoid) (5)	6 (13%)
Outcome*	Discharged – follow up Exitus Follow up with ostomy	35 (76%) 3 (6%) 8 (17%)

Data are given as median (min-max) or number (percent). Abbreviations: C/S, cesarean section; PNA, postnatal age; NEC, necrotizing enterocolitis; ASD; atrio septal defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; MR, mitral regurgitation; TR, tricuspid regurgitation; VSD, ventricular septal defect; CRP, C-reactive protein.
*Categorical variables compared with Chi-Square.

The detailed characteristics of post-NEC strictures patients were summarized in Table 2. When we compared the post-NEC strictures patients with the patients who underwent surgery for NEC, we obtained significant results only at the age of surgery (p=0,024). While the median surgery day of post-NEC strictures was 39 days; the median surgery day of patients who underwent surgery for NEC was 18 18,5 days. In total, all treatment processes of our 35 patients have been completed, we have lost 3 of our patients, and 8 of our patients are still undergoing treatment with ostomy.

Discussion

NEC remains a significant gastrointestinal emergency and source of morbidity in preterm infants, with an incidence ranging from 3% to 7%, linked to gestational age (GA) at birth, and mortality rates as high as 50% (3-6). The complications of NEC encompass gastrointestinal issues such as strictures or adhesions, neurodevelopmental delay, and cholestasis (7). Post-NEC strictures, one of these complications, can manifest both after recovery from the acute phase of NEC and in surgically treated NEC patients.

Table 2. Comparative table of survivors with and without post-NEC strictures.			
Variable	**Post-NEC strictures + (n=6)**	**Post-NEC strictures – (n=40)**	**p-value**
Male*	4 (%66)	27 (%67)	1.000
Gestational age (week)	29 (23-40)	30 (24-40)	0.831
Mother age (year)	27 (23-41)	31 (20-45)	0.233
Birth weight (g)	1065 (490-2720)	1097 (505-4160)	0.599
Type of birth (C/S)*	4 (%66)	38 (%95)	0.770
Postnatal age of NEC diagnosis (days)	6 (2-23)	6 (2-39)	0.782
pH at onset of NEC	7,31 (7,20-7,40)	7,30(7,02-7,39)	0.727
First CRP after onset symptoms (mg/L)	4 (0-11)	2 (0-150)	0.591
Leukocytes at onset of NEC (10^9/L)	11 (5-11)	7 (1-15)	0.422
Hemoglobin at onset of NEC (mmol/L)	12 (6-14)	14 (8-18)	0.125
Thrombocytes at onset of NEC (10^9/L)	182 (109-409)	186(50-376)	0.846
Surgery age (day)	39 (18-90)	18 (2-50)	0.024
CRP before surgery (mg/L)	3 (0-19)	2 (0-105)	0.932
Leukocyte before surgery (10^9/L)	7 (3-13)	7(1-17)	0.807
Hemoglobin before surgery (mmol/L)	11 (10-12)	9 (8-17)	0.832
Thrombocytes before surgery (10^9/L)	209 (11-444)	155 (50-419)	0.247
Outcome*			
Discharged – follow up	4 (%66)	31 (%77)	0.557
Exitus	1 (%16)	2 (%5)	
Follow up with ostomy	1 (%16)	7 (%17)	

Data are given as median (min-max) or number (percent).
Statistically significant result is indicated in bold and italic ($p<0.05$).
Continuous variables were compared with the Mann Whitney U test.
*Categorical variables compared with Chi-Square.

Intestinal strictures are first described by Rabinowits et al. (8,9) in 1968 with colonic findings in newborns affected by NEC. Later, intetsinal stricture series after NEC began to be published in the literature. In different series, the incidence of post-medical or postoperative stricture varies between 3% and 65%, and the overall incidence is given as 20% (3, 4,7,8). In our study, we included patients developing intestinal strictures after medical NEC treatment, with only 6 out of 395 patients (approximately 1.5%) affected, a rate lower than reported in the literature. This discrepancy might be attributed to our single-center study.

Although we observed higher CRP values in patients operated for post-NEC strictures during both NEC diagnosis and pre-operation compared to those undergoing surgery for primary NEC, statistical significance eluded us. This aligns with findings by Heida et al. (2), who discovered significant CRP value differences in patients with post-NEC strictures. Also Phad et al. (6) observed significant association between presence of high white cell count during acute NEC and length o-f bowel resected at NEC surgery and the occurrence of intestinal strictures and Zhang et al (3) predicted both leukocyte and CRP values may be associated with stricture formation. In our study, mean leukocyte values were found to be high and mean platelet values were low in post-NEC stricture patients, and no significant results could be obtained when compared with patients who underwent surgery due to primary NEC. However, this situation makes us

think that inflammation may be an important factor in the development of strictures.

Various factors contribute to the development of intestinal strictures after NEC, such as septicemia, perforation, intestinal obstruction, illness severity, congenital anomalies, mechanical ventilation duration, fasting duration, milk volume tolerance, and hospital stay length (3, 8-10). In the pathophysiology of strictures, interruptions in blood flow within the intestinal wall lead to ischemia, triggering inflammatory reactions, collagen deposition, fibrosis, wound contraction, and intravascular thrombosis (4, 6,10). We obtained significant results in patients comparing the time of primary surgery due to NEC with the time of surgery due to stricture after NEC. We think that this may depend on the time of formation of the stricture.

In our study, we found that the stricture occurred especially in the colon and primarily in the descending colon and sigmoid colon. Studies have shown that the colon (80%) is the commonest site for post-NEC stricture and mostly left colon and especially splenic flexura followed by terminal ileum in 15% of cases. (6, 8,10,11). Even Wiland et al. (10) emphasized that multiple strictures may be present (15%) one in their study.

Mean values of gestational age weeks and birth weights were found to be lower in our patients who developed stricture after post-NEC; but we could not obtain statistically significant results. However, we still think that prematurity and low birth weight may be an important factor in the development of strictures after NEC. In our study, we could not obtain significant results since most of our patients (91.3%) were born by cesarean section, but Zhang et al.(3) found that the cesearean delivery was significantly correlated with the occurence of strictures in their study.

In many studies, researchers recommend contrast barium radiography as the first choice for diagnosing suspicious patients, since the majority of pot-NEC strictures are in the colon (4,10-12). The diagnosis of our patients who developed strictures was made with a contrast enema, and a colostomy or ileostomy was performed first and then their ostomies were closed. We also did mucosal biopsy to exclude congenital megacolon for all patients.

Most researchers emphasize the importance of inflammatory process in the evolution of intestinal lesions as well the role of biological markers such as CRP, leukocyte in the overall prognosis of NEC. Liu et al (4) report a rare case of an immunocompetent term newborn with post-NEC stenosis requiring surgical intervention, associated with CMV infection.

Conclusion

In conclusion, the possibility of stricture development after NEC should definitely be considered in patients with prolonged feeding intolerance, distention, gastric residual and even rectal bleeding. Therefore, close follow-up and multidisciplinary approaches are very important, and contrast barium radiography should be performed first for diagnosis.

Ethics

Ethics Committee Approval: Karadeniz Technical University Faculty of Medicine between January 2009 and December 2021. Ethical approval for data collection review was obtained from the local ethical committee (date: 06.01.2020 decision no: 2019-337).

Conflict of Interest: No conflict of interest was declared by the authors.

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