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Comparison of cardiogenic NEC and classical NEC in the fourth level neonatal intensive care center

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Abstract

Background The most common inflammatory gastrointestinal disorder in newborn infants is necrotizing enterocolitis (NEC). Despite the multifactorial etiology of NEC, its pathogenesis is the same regardless of the etiology—a decrease in enteric perfusion that results in enteritis, dysmotility, necrosis, and sepsis. This study aims to evaluate whether the characteristics of NEC in infants with congenital heart disease (CHD) are different from those of classical NEC.

The records of 39 NEC patients were reviewed retrospectively. Based on the presence or absence of CHD, the patients were divided into two groups. The group with NEC and CHD was named cardiogenic NEC and the other group was named classical NEC. The two groups were compared in terms of mode of delivery, gestational age, birth weight, age at onset of NEC, surgical treatment rate, NEC localization, and mortality rate.

Results The cardiogenic NEC group consisted of 25 patients, and the classical NEC group consisted of 14 patients. The results indicate that there were no differences between the two groups in terms of sex, mode of delivery, and location of the NEC. There were higher levels of gestational age, birth weight, and age at which NEC was diagnosed in the cardiogenic group. The mortality rate of the cardiogenic NEC group (72%) was higher than that of the classical NEC group (28.6%). In addition, the surgical treatment rate of the cardiogenic NEC group (84%) was higher than that of the classical NEC group (57.2%).

Conclusions The clinical course of NECs with CHD is different from that of classical NEC. In NEC, CHD can be identified as an important risk factor.

Keywords Congenital heart disease, Necrotizing enterocolitis, Neonatal intensive care

Background

Necrotizing enterocolitis (NEC), which has a high morbidity and mortality rate, is the most common inflammatory gastrointestinal disorder of newborn infants. Although it is more common in premature infants (13%), it can be observed in term and near-term neonates [1]. Presently, the etiopathogenesis of NEC is unknown [1–4]. It should be noted, however, that there are various factors that may contribute to NEC, including prematurity, low birth weight, immaturity of the gastrointestinal tract, intestinal hypoxia, and ischemia [1, 5–7]. Term neonates with CHD are thought to be at higher risk of NEC because of poor mesenteric artery perfusion [1, 8–12]. Additionally, it has been observed that the risk of developing NEC in premature infants increases with the severity of CHD [9, 13]. NEC with CHD has been proposed to differ from classical NEC in terms of onset time,

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localization, clinical course, and outcomes [8]. Although the etiology of NEC is mainly multifactorial, the pathogenesis is the same in all etiological scenarios—the decrease in enteric perfusion leading to enteritis, dysmotility, necrosis, sepsis, and so on. Therefore, our study aims to evaluate whether the characteristics of NEC in neonates with CHD are different from those of classical NEC.

Methods

A retrospective review of 189 records of neonatal intensive care patients treated at our hospital between October 2017 and December 2020 was conducted. The patients were classified based on the Bell staging system. Patients with irregular body temperature, gastric residual, vomiting, abdominal distention, occult blood in the stool, and standard or dilated bowel loops on abdominal X-ray were considered stage I.

In addition to the findings in stage I, patients with gross blood in the stool and mild metabolic acidosis, radiological pneumatosis intestinalis, or gas in the portal vein were considered stage II.

The patients in whom hypotension, and apnea bradycardia were added to the findings in stage II; and ascites or pneumoperitoneum were observed in the radiological imaging were evaluated as stage III [14].

Patients with stage ≥ II NEC were included in the study. A total of 27 patients with stage I NEC or suspected NEC were excluded from the study, of which 16 were in the cardiogenic group and 11 were in the classical NEC group.

The Institutional Ethics Committee approved the present study.

The patients were divided into two groups based on the presence or absence of accompanying CHD. A group of patients with NEC and accompanying CHD is called the cardiogenic NEC group, whereas a group of patients with classical NEC is called the classical NEC group. Gender, birth weight, gestational age, hospitalization, diagnoses, feeding pattern, upright abdominal X-ray, laboratory results, echocardiography, and ultrasonography reports of the patients were recorded. In addition, the patient's age (at diagnosis, operation status (whether a cardiac or intestinal operation was conducted), operative findings, NEC localization, clinical course, and results were investigated. A comparison was made between the two groups regarding mode of delivery, gestational age, birth weight, age at onset of NEC, operation rate, operative findings, NEC localization, and mortality rate.

Statistical methods

Statistical analysis was performed using SPSS (Social Sciences software package version 22.0). Categorical variables were expressed in numbers (n) and percentages (%). Numerical variables with a normal distribution are expressed as the mean standard deviation. Student's t test and Mann–Whitney U test were used to compare variants in NECs with and without CHD. A p value less than 0.05 was considered statistically significant.

Results

A total of 39 NEC patients, 25 with CHD (cardiogenic; tetralogy of Fallot ($n=4$), transposition of the great arteries ($n=2$), pulmonary stenosis ($n=1$), VSD ($n=3$), ASD ($n=4$), AVSD ($n=1$), PDA and PFO ($n=4$), PDA ($n=4$), PFO ($n=2$)), and 14 without CHD (classical), were included in our study. On the first day, the patients were started on breast milk. Three patients were diagnosed with antenatal CHD. Cardiac surgery was performed in only three of the patients with CHD. Two of these patients developed NEC during the postoperative period and one developed NEC before surgery. While 12% of patients with cardiogenic NEC were stage II and 88% were stage III, 35.7% of patients with classical NEC were stage II, and 64.3% were stage III.

Among the cardiogenic group, six patients were female, 19 were male, and 32% were born vaginally. In the classical group, six patients were female, eight were male, and 35.7% were born through vaginal delivery. There was no significant difference between the two groups regarding gender and mode of delivery ($p>0.05$).

There was a significant difference in gestational age between the cardiogenic and classical groups (mean = 32.4 ± 5.8 weeks) ($p<0.05$). Likewise, the cardiogenic group had a higher average birth weight (1934.3 ± 799.2 g) than the classical group (mean = 1016.6 ± 319.7 g) (p 0.05). A higher prevalence of NEC was observed in neonates with cardiogenic NEC at the age of 24.1 days (medical error $p=0.05$) than in neonates with classical NEC at the age of 12.9 days (medical error $p=0.05$).

The cardiogenic group had a higher rate of surgery ($p=0.01$); 84% had a laparotomy and 4% had a bedside drain inserted. In the classical group, 57.2% of the patients had a laparotomy, and 7.1% had a bedside drain installed. Among the patients in the cardiogenic group, the small intestine was involved in 32% of cases, the colon in 40% of cases, and both the small intestine and colon in 8% of cases. A total of 80.9% of these patients had perforations (colon 42.8%, small intestine 38.1%), and 19.1% had transmural necrosis (colon 4.7%, small intestine 14.2%).

In the classical group, 42.8% of patients had small intestine involvement, while 14.2% had colon involvement. In this group, 75% of patients had perforations (25% in the colon, 50% in the small intestine) and 25%

had transmural necrosis in the small intestine. Regarding the involved intestinal section, there was no difference between the two groups. The most significant observation was that the mortality rate of the cardiogenic group (72%) was higher than that of the classical group (28.6%) ($p < 0.05$) (Table 1).

Discussion

With its high morbidity and mortality rates, NEC has emerged as one of the most destructive diseases in neonatal intensive care units. Although the exact etiology of NEC remains unknown, research states that it is multifactorial, with intestinal ischemia as one of the factors. There was a perception that the mode of delivery could be a contributing factor to ischemic trauma; however, studies have failed to find a connection between the mode of delivery and NEC [15]. It has been confirmed by our study that infants with cardiogenic and classical NEC are not different in their modes of delivery, and that therefore mode of delivery alone does not constitute a risk factor for the development of NEC in patients with CHD.

Another critical factor affecting the development of NEC is nutrition. Breast milk is a known protective factor in the prevention of NEC (this may be due to the presence of bioactive substances with bactericidal and immune-modulating properties) [6], and feeding with breast milk during the first week can lower the frequency of NEC that occurs in the early period [16]. In another study, preoperative feeding with breast milk was found to reduce the occurrence of NEC in infants with CHD [5]. Therefore, in our hospital, infants with CHD whose preoperative condition is stable and preterm and term infants are routinely fed breast milk. Additionally, equal importance is given to nutrition in the early postcardiac surgery period. Our research did not indicate any difference in patients' nutritional patterns in the cardiogenic and classical groups. In several studies, it has been demonstrated that both preterm and term infants with CHD are at a higher risk of developing NEC as a result of intestinal hypoxia and ischemia during the first few days after birth [9, 10]. In term infants with CHD, persistent retrograde diastolic flow in the abdominal aorta is associated with an increased risk of NEC [17]. In our study, 28% of patients in the cardiogenic group developed intestinal hypoxia due to cyanotic heart disease. Moreover, the number of patients in the cardiogenic group was higher

Table 1 Characteristics of patients included study

Characteristics	Cardiogenic NEC 25 n(%)	Classical NEC 14 n(%)	*P* value
Gender			0.365
Female	6 (24)	6 (42.8)	
Male	19 (76)	8 (57.1)	
Mode of delivery			0.920
Vaginal	8 (32)	5 (35.7)	
Caesarean section	17 (68)	9 (64.2)	
Median gestasyon age (week)	32.4 ± 5.8 (22–39)	26.5. ± 3.1 (22–32)	**0.003**
Mean birth weight (g)	1934.3 ± 799.2 (700–2900)	1016.6 ± 319.7 (750–1700)	**0.0005**
Age at disease onset (days)	24.1 ± 18.7 (7–81)	12.9 ± 7.6 (4–28)	**0.027**
Treatment			**0.002**
Ileostomy	9 (36)	6 (42.9)	
Colostomy	9 (36)	2 (14.3)	
Resection and anastomosis	3 (12)	0 (0)	
Bedside peritoneal drain	1 (4)	1 (7.1)	
Medical treatment	3 (12)	5 (35.7)	
Location of NEC			0.154
Small intestine	8 (32)	6 (42.8)	
Colon	10 (40)	2 (14.2)	
Pan-intestinal	2 (8)	0 (0)	
Outcome			0.162
Survival	7 (28)	10 (71.4)	
Mortality	18 (72)	4 (28.6)	

NEC Necrotizing enterocolitis

than that in the classical group, which indicates that CHD directly increases the frequency of NEC.

A comparison was also made between the gestational age of infants in the cardiogenic and classical groups. Pickard et al. reported no difference in the gestational age of NEC infants with or without CHD [11]. Another study found that infants with CHD who developed NEC had a greater gestational age than those without CHD who developed NEC [8]. There is no doubt that infants with very low birth weights are at an increased risk of developing NEC. In their study, Fisher et al. reported that the frequency of NEC is inversely proportional to birth weight in infants with CHD [9]. In the present study, the results indicate that the gestational age and birth weight of term and near-term infants with CHD differ significantly from those observed in infants without CHD [8]. The results of our study suggest that NEC cases accompanied by CHD have a different clinical course than classical NEC cases. Based on these findings, it can be concluded that the molecular mechanisms responsible for the development of NEC are different in patients with CHD.

NEC appears to present at 12 days in preterm infants [15], 8 days in term infants, and 26 days in term infants with CHD [18]. According to Lambert et al., the onset of NEC in infants with CHD occurs seven days after birth [19]. In some studies, as in our study, the age of onset of NEC was found to be higher in infants with CHD than in infants without CHD [8, 11]. Therefore, as per our study, infants with CHD should be actively monitored in the third week of life to develop NEC.

It is well known that cardiac surgery increases the risk of developing NEC, although some infants with CHD develop NEC prior to surgery as a result of reduced mesenteric perfusion [8]. Many factors contribute to this increased risk, such as stress following cardiac surgery, systemic inflammatory responses, hypothermia, decreased blood flow to the intestinal mucosa, and an increase in intestinal permeability postoperatively [8, 13, 20]. However, in our study, only two patients developed NEC after cardiac surgery. Therefore, we concluded that the risk of NEC in infants with CHD is higher even without surgery.

Different opinions have been expressed regarding the localization of NEC in infants with CHD. Some studies indicate no difference in the localization of NEC in infants with and without CHD [8, 21], whereas Diez et al. reported that the small intestine is more affected in infants with CHD [22]. However, in another study, NEC was most frequently observed in the colon of infants with CHD [23]. There may be several reasons for this, including pulmonary steal and ischemia-sensitive intestines distal to the splenic flexure and rectosigmoid arteries [10, 23]. The results of our study also indicate no relationship between NEC localization and CHD. Nevertheless, our research findings are limited to observations made on operated patients. Hence, to determine the localization of NEC in infants with CHD, further studies are needed in which the affected bowel segment can be evaluated in nonoperated patients.

Complications, such as perforation and stricture, are more common in classical NEC patients because the preterm infants' intestines are immature and more fragile; infants with CHD are often at or near term, thereby reducing the requirement for surgical treatments [8]. Another study reported that the prevalence of CHD in NEC patients did not affect the rate of surgery, complications, or mortality [23]. However, in our study, more surgical treatments were performed in infants with CHD. Our results indicate that bedside drain installation was higher in the noncardiogenic group. This was because the general condition of the noncardiogenic NEC group cases was too bad to be anesthetized. Therefore, it can be concluded that NEC infants with CHD have a different course of the disease and require different surgical interventions than those with classical NEC.

Some studies have reported that the mortality rate of NEC patients is higher in infants with NEC and severe CHD [8, 13, 18]. Kesler et al. found that patients with NEC accompanied by CHD had longer hospitalization [24], and their mortality rate was sevenfold higher than that of patients with NEC. Pickard et al. demonstrated that infants with CHD had superior short-and long-term outcomes [11]. Our study found that the mortality rate of the cardiogenic group was higher than that of the classical group. In NEC patients, the mortality rate increases with comorbid diseases, such as CHD.

Limitations

The limitations of our study are the small number of patients and its single center and retrospective structure.

Conclusion

CHD can be identified as an essential risk factor for NEC. CHD-related NECs differ from classical NECs in terms of body weight, gestational age, age of onset, surgical treatment requirement, and mortality rate.

Abbreviations

NEC	Necrotizing enterocolitis
CHD	Congenital heart disease
VSD	Ventricular septal defect
ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale

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Authors' contributions
T.Ö., S.B., and N.M.O contributed to the literature search and the study design. T.Ö., S.B., and N.M.O. contributed to the data collection, statistical data analysis, and data interpretation and the drafting manuscript and approved the final version. All authors have read and approved the manuscript.

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Availability of data and materials
The datasets (SPSS files) used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Clinical Studies Ethics Committee of Health Sciences University (11.06.2021/ number:785). Since the study was of a retrospective nature, informed consent was not obtained from the participants. However, written informed consent was obtained from the parents of the patients for the examinations and treatments to be performed upon arrival at the hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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