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Research Article

Variation in Epidemiological Characteristics, Therapeutics Strategies and Main Outcomes between Neonates with Necrotizing Enterocolitis Diagnosed Consecutively, During the Period 2003-2015

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Received: May 13, 2019; **Published:** June 25, 2019

Abstract

Background: Necrotizing enterocolitis is one of the most common gastrointestinal emergencies in the neonatal period. The epidemiological profile of the potential patient affected by NEC is constantly changing.

Objectives: The aim of this study is to examine the variation in epidemiological characteristics, therapeutic strategies and outcomes between neonates diagnosed during the periods 2003 - 2009 and 2010 - 2015.

Methods: A total of 124 patients were included in the study. Information was obtained from medical records and included patient demographics characteristics, prenatal information, radiological findings, analytical data and therapeutic management.

Comparisons for quantitative variables were made using Student's t-test or the Mann-Whitney U-test, depending on which was appropriate after checking for normality using the Kolmogorov-Smirnov-test. Associations between qualitative variables were analyzed using Pearson's chi-squared-test.

Results: The median gestational age was 33 weeks. There was a significant decrease in prophylactic antibiotic treatment, mechanical ventilation and umbilical catheterization during these periods. During the second period, the rate of surgical treatment decisions increased significantly (29,4% vs 57.9%), and a relevant decrease in mortality was identified (14% vs. 5.3%).

Conclusions: This study shows an important variation in epidemiological and clinical characteristics of patients with necrotizing enterocolitis in the recent years. The medical and surgical strategies changed during follow-up too.

Keywords: *Enterocolitis; Necrotizing; Neonatology*

Introduction

Necrotizing enterocolitis (NEC) is an ischemic and inflammatory disease mostly seen in preterm infants. It is the most serious gastrointestinal complication of prematurity and the associated mortality is high [1-3].

The first case reports of NEC were published in the first half of the 19th century, but it was with the development of neonatal intensive care units (NICUs) in the 1960s when the condition became more common and was described as a clinical, radiographic and pathologic entity [4].

Survival of premature infants has increased dramatically over the past decades due to improved perinatal and neonatal care [5]. There are concerns that this may lead to increased incidence rates of morbidities specific to the premature infant, for example necrotizing enterocolitis [6] and this increase in survival, changes the general characteristics of potential patients affected by NEC.

Reports of trends in the incidence of NEC are, however, contradictory, showing both increasing [7] and decreasing rates [8,9]. Marked variability is evident across NICUs and countries [10,11].

Multitudes of factors have been proposed to be associated with the development of NEC. But only prematurity has been consistently associated [12,13].

Although it is one of the most life-threatening diseases affecting neonates, we still do not completely understand the pathogenesis or how to prevent or treat the disease.

Despite an increase in the quality of available evidence regarding NEC, there remains a wide variation in medical and surgical management and outcomes [14,15].

Its clinical presentation is highly variable ranging from feeding intolerance or abdominal distention to fulminant shock and death. The etiology of NEC is not clear and its treatment can be difficult. There is no effective universally accepted prevention strategy; therefore early detection and appropriate treatment of NEC are essential to minimize the morbidity and mortality of this condition.

There is a general agreement that surgical intervention for necrotizing enterocolitis is required for intestinal gangrene [16]. Ideally, surgery would be performed as soon as intestinal gangrene is present; however determining the presence of gangrene continues to be difficult [17]. This is most evident when gangrene has led to perforation and pneumoperitoneum, but these findings are usually the final events of the illness.

For this reason, NEC is one of the most frequent causes for emergent surgical intervention in infants [12].

Many individual findings have also been noted that often indicated the presence of necrosis. There have been many attempts at developing criteria to determine the need for surgical intervention in patients with NEC [17,18]. However, the need for surgery in these complex patients and the clinical course remains unclear.

The optimal treatment for necrotizing enterocolitis is a common challenge for pediatric surgeons. Although many studies have evaluated prevention and medical treatment for NEC, few guidelines for surgical management exist [19].

A very recent study, which tries to define patterns in the management of NEC conducted by the EUPSA (European Society of Pediatric Surgeons), concludes that many aspects of NEC management are lacking consensus and surgeons differ especially over surgical treatment and postoperative management [20].

There is a high variability and uncertainty in the prevention, prevalence, diagnosis and therapeutic strategies of the disease. The aim of this study is to examine the variation in epidemiological characteristics, prenatal, clinical and radiological findings, relevant laboratory information, therapeutic management and events (death, stenosis, perforation) during the periods 2003 - 2009 and 2010 - 2015.

Material and Methods

A total of 124 patients were consecutively included in the study who were diagnosed at the University Hospital Complex in A Coruña, Spain between 2003 and 2015. A retrospective review of the patients' medical records was carried out together with a follow-up of a mean of 2.5 ± 5.1 months. These patients generated a total of 304.9 months of follow-up. We collected information on sociodemographic variables, radiological findings, gestational data, perinatal history, clinical, analytical and perinatal therapeutic management and subsequent events: mortality, perforation and stenosis in patients with necrotizing enterocolitis during the follow up.

A diagnosis of NEC was made based on clinical, radiological and/or histopathological evidence of stage II, III or IV NEC according to Bell's modified criteria [9].

We excluded patients who did not meet criteria for inclusion in the study; those who were referred from other centers without baseline data for diagnosis of NEC, those with intraoperative finding of focal intestinal perforation or those who did not sign the informed consent.

This sample size (n = 124) makes it possible to estimate the parameters of interest with a confidence interval (CI) of 95% ($\alpha = 0.05$) and a precision of ± 8.9%. A descriptive study was made of the included variables. The quantitative variables were expressed as mean ± standard deviation (SD), while the qualitative variables were expressed as an absolute n value and the percentage, with estimation of the 95% confidence interval. Comparisons for quantitative variables were made using Student's t-test or the Mann-Whitney U test, depending on which was appropriate after checking for normality using the Kolmogorov-Smirnov test. Associations between qualitative variables were analyzed using Pearson's chi-squared test.

The study was carried out according to the principles laid down in the Declaration of Helsinki and ensuring compliance with Spanish Decree 29/2009, which regulates the use of and access to electronic medical records. Informed consent was obtained from all individual participants included in the study.

Results

The changes detected during the follow-up are shown in table 1.

Variables	Period 2003 - 2009 (n = 86)		Period 2010 - 2015 (n = 38)		p
	Mean ± SD	n (%)	Mean ± SD	n (%)	
Gender					0,065
Male		58 (67,4%)		19 (50%)	
Female		28 (32,6%)		19 (50%)	
Mother´s age (years)	31,13 ± 6,15		34 ± 5,9		**0,020**
Type of fecundation					0,128
Spontaneous		75 (87,2%)		29 (76,3%)	
Artificial		11 (12,8%)		9 (23,7%)	0,13
Type of gestation					0,895
Singletons		71 (82,6%)		31 (81,6%)	
Multiple		15 (17,4%)		7(18,4%)	
Type of delivery					0,803
Vaginal		50 (58,1%)		23 (60,5%)	
Caesarean		36 (41,9%)		15 (39,5%)	
Gestational age (weeks)	32,80 ± 4,14		33,58 ± 4,43		0,35
Categories of gestional age		**n (%)**		**n (%)**	0,89
< 30 weeks		19 (22,1%)		7 (19,4%)	
30 - 34 weeks		37 (43%)		14 (38,8%)	
35 - 37 weeks		18 (20,1%)		6 (16%)	
38 weeks or more		12 (13,9%)		9 (25%)	
Birth weight (grams)	1793,47 ± 781,6		2053,63 ± 847,1		0.099
Categories Birth weight		**n (%)**		**n (%)**	0.412
< 1000 grams		15 (17,6%)		7 (18,4%)	
1000-1499 grams		16 (18,8)		3 (7,9%)	
1500- 2499 grams		42 (49,4%)		20 (52,6%)	
2500 grams or more		12 (14,1%)		8 (21,1%)	
Oligoamnios		17 (19,8%)		3 (7,9%)	0,97
Associated syndrome		2 (2,3%)		1 (2,6%)	0,919
Antenatal steroids		36 (41,9%)		14 (36,8%)	0,599
Intrauterine restrictive growth		18 (20,9%)		5 (13,2%)	0,305
Bradichardy		16 (18,6%)		11(28,9%)	0,198
Respiratory distress		39 (45,3%)		20 (52,6%)	0,454
Apgar 1´	7,06 ± 1,9		7,4 ± 1,9		0,197
Apgar 5´	8,2 ± 1,4		8,5 ± 1,9		0,071
Treatment strategies					
Umbilical catheterism		50 (58,1%)		15 (39,5%)	0,55
Transfusion		15 (17,4%)		6 (15,8%)	0,821
Prophylactic antibiotic		65 (75,6%)		25 (65,8%)	0,26
Perinatal treatment: surfactant		24 (27,9%)		7 (18,4%)	0,26
Mechanic ventilation		32 (37,2%)		9 (23,7%)	0,14
Hours of mechanic ventilation	119,67 ± 197,8		127 ± 126,23		

Table 1: *General characteristic of the sample study in different periods.*

The average gestational age of our series of cases was 33 ± 4.2 weeks and it remained stable in both periods 32.8 weeks vs. 33.5 weeks.

In the second period of our study, the rate of newborns > 38 weeks affected by NEC increased from 14% in the first period to 25% in the second and was stable in the other subgroups.

The weight remained stable in both periods.

During the two study periods, 2003 - 2009 and 2010 - 2015, there was a progressive and significant increase in maternal age 30.69 ± 6.3 years vs. 34.09 ± 5.5 years.

Analytical differences between periods are shown in table 2. Preoperative acidosis had a relevant decrease from 69% in the first period to 28% in the second.

Variables	Period 2003 - 2009 (n = 86)		Period 2010 - 2015 (n = 38)		p
	Mean ± SD	n (%)	Mean ± SD	n (%)	
Hematocrit at diagnosis (%)	40,97 ± 8,40		45,13 ± 11,0		0.025
Presurgical hematocrit (%)	36,19 ± 6,3		39,64 ± 7,6		0.141
Hemoglobin at diagnosis (g/dL)	13,97 ± 2,84		15,40 ± 3,82		0.030
Presurgical Hemoglobin (g/dL)	12,47 ± 2,21		13,42 ± 2,70		0.242
Ph at diagnosis	7,34 ± 0,09		7,34 ± 0,08		0.930
Presurgical Ph (categories)					0.022
pH ≤ 7,3		9 (69,2%)		5 (27,8%)	
pH > 7,3		4 (30,8%)		13 (72,2%)	
Platelets at diagnosis (categories) (x 10^9/L)					0.586
60000 or less		4 (5,0%)		1 (2,8%)	
> 60000		76 (95%)		35 (97,2%)	
Presurgical platelets (categories) (x10^9/L)					0.927
60000 or less		4 (23,5%)		4 (22,2%)	
> 60000		13 (76,5%)		14 (77,8%)	
Glycemia at diagnosis (mg/dL)	100,38 ± 56,1		106,97 ± 54,10		0.572
Presurgical Glycemia (mg/dL)	98,21 ± 66,60		95,94 ± 38,34		0.906

Table 2: *Analytical differences between periods.*

At the time of diagnosis for patients in the second period, they presented less thrombocytopenia and better hematocrits. Hematocrit increased from 40.97 ± 8.40% to 45.13 ± 11.0%. Platelets less than 60,000 10^9/L decreased from 5.0% to 2.8%.

Between periods, there were significant statistical differences in the clinical manifestations of this pathology, whereas erythema of the abdominal wall, gastric residue and bilious vomiting at diagnosis was more prevalent in the second period (Table 3).

Variables	Period 2003 - 2009 (n = 86)	Period 2010 - 2015 (n = 38)	p
	n (%)	n (%)	
Fever at diagnosis	38 (44,7%)	12 (31,6%)	0,17
Presurgical fever	9 (36%)	4 (18,2%)	0,17
Apnea at diagnosis	26 (30,6%)	15 (39,5%)	0,33
Presurgical apnea	12 (46,2%)	9 (40,9%)	0,71
Pain at diagnosis	27 (22,1%)	18 (47,4%)	0,107
Presurgical pain	23 (88,5%)	17 (77,3%)	0,30
Abdominal distension at diagnosis	86 (100%)	38 (100%)	-
Presurgical abdominal distensión	26 (100%)	22 (100%)	-

Erythema at diagnosis	0 (0%)	3 (7,9%)	**0,009**
Presurgical erythema	8 (30,8%)	8 (36,4%)	0,682
Tenderless at diagnosis	9 (10,6)	1 (2,6%)	0,136
Presurgical tenderless	17 (68,0%	9 (40,9%)	0,062
Lethargy at diagnosis	44 (52,4%)	20 (54,1%)	0,86
Presurgical lethargy	19 (76,0%)	13 (65,0%)	0,42
Irritability at diagnosis	5 (16,7%)	10 (34,5%)	0,12
Presurgical irritability	0 (0%)	2 (12,5%)	0,24
Abdominal mass at diagnosis	2 (2,4%)	0 (0%)	0,34
Presurgical abdominal mass	1 (3,8%)	1 (4,5%)	0,90
Blood in stools at diagnosis	84 (98,8%)	36 (94,7%)	0,17
Presurgical blood stools	25 (100%)	21 (95,5%)	0,28
Gastric residue at diagnosis	47 (56,0%)	33 (86,8%)	**0,001**
Presurgical gastric residue	17 (65,4%)	19 (86,4%)	0,094
Bilious vomiting at diagnosis	9 (10,7%)	10 (26,3%)	**0,028**
Bilious presurgical vomiting	1 (3,8%)	0 (0%)	0,35

Table 3: *Clinical manifestations between periods.*

Although no statistical differences were observed, we identified a decrease in the second period of fever at diagnosis and preoperatively, and a decrease in preoperative abdominal tenderness.

In the radiological findings, we noticed in the second study period a significant increase in the absence of intraabdominal gas at diagnosis and a decrease in preoperative pneumatosis. No statistical differences were found preoperatively, but we registered a relevant decrease in the fixed loop and the ileus (Table 4).

Variables	**Period 2003 - 2009 (n = 86)**	**Period 2010 - 2015 (n = 38)**	**p**
	n (%)	**n (%)**	
Dilated loops at diagnosis	86 (100%)	37 (97,4%)	0,13
Presurgical dilated loops	24 (96%)	20 (100%)	0,37
Fixed loop at diagnosis	2 (2,3%)	2 (5,3%)	0,39
Presurgical fixed loop	7 (26,9%)	3 (15%)	0,33
Absence of intraabdominal gas at diagnosis	3 (3,5%)	6 (15,8%)	**0,015**
Presurgical absence of intraabdominal gas	5 (19,2%)	1 (5,0%)	0,15
Ileus at diagnosis	13 (15,1%)	4 (10,5%)	0,49
Presurgical ileus	8 (30,8%)	3 (15%)	0,21
Free intrabdominal fluid	3 (3,5%)	0 (0,0%)	0,24
Presurgical free fluid	2 (7,7%)	1 (5,0%)	0,71
Pneumatosis at diagnosis	42 (48,8%)	12 (31,6%)	0,07
Presurgical pneumatosis	21 (80,8%)	9 (45%)	**0,012**

Table 4*: Radiologic features between periods.*

Therapeutic strategies changed with a relevant decrease in the use of prophylactic antibiotics (75,6% vs. 65,8%), umbilical catheterization (58.1% vs. 39.5%), transfusions (17.4% vs. 15.8%) and invasive mechanical ventilation (37.2% vs. 23.7%).

Surgical management has increased from 29.4% in the first period to 57.9% in the second period. In the intraoperative findings, we found an important rise in white laparotomies with normal gut from 0% to 4.5%. Necrosis decreased from 64% to 54.5%.

During follow-up, the mortality rate in the first period was 14% and 5.3% in the second period. The percentages of stenosis and perforation were similar in both periods (Table 5).

Variables	Period 2003 - 2009 (n = 86)	Period 2010 - 2015 (n = 38)	p
	n (%)	n (%)	
Treatment			**0,002**
Medical management only	61 (70,6%)	16 (42,1%)	
Surgical management	25 (29,4%)	22 (57,9%)	
Drainage	6 (24%)	9 (40,1%)	0,21
Resection and anastomosis	0 (0%)	1 (4,5%)	0,272
Resection < 15 cm	12 (48%)	6 (27,3%)	0,145
Resection > 15 cm	7 (28%)	7 (31,8%)	0,775
Intraoperative findings			
Normal gut	0 (0%)	1 (4,5%)	0,272
Reversible ischemic gut	6 (24%)	8 (36,3%)	0,355
Necrosis	16 (64%)	12 (54,5%)	0,11
Simple intestine perforation	9 (36%)	6 (27,3%)	0,402
Multiple intestine perforation	9 (36%)	3 (13,6%)	0,655
Events in the follow up			
Death	12 (14%)	2 (5,3%)	0,16
Stenosis	5 (5,8%)	3 (7,9%)	0,664
Perforation in the follow up	8 (9,3%)	3 (7,9%)	0,799

Table 5: *Therapeutic strategies between periods.*

Discussion

This study presents the variation in epidemiological characteristics, therapeutics strategies and main outcomes between neonates diagnosed consecutively between periods (2003 - 2009 and 2010 - 2015).

It describes the changes in mothers and the patients' profile during these years, as well as the different treatments administered and the outcomes of the patients with necrotizing enterocolitis in the study.

According to the published literature [21], there was a slight predominance in male gender in the first period, equaling from 67.5% to 50% in the second period.

The mother's epidemiological profile has changed in the second period with a significant increase in the average age and the rate of artificial gestation. This fact shows the advances in assisted reproduction and the increase in the aging mothers in developed countries [22].

In our series, this increase is not related to an increase in prematurity, the rate of intrauterine growth restriction or a decrease in the weight at birth.

As other recent series reported, in concordance with our report, gestational age or birth weight of newborns affected by NEC has remained stable in recent years [23,24], despite other studies which reveal an increase in prematurity and low weight for these patients [25].

All this variability explains, the fact that, the potential patient affected by NEC remains unclear and the characteristics are constantly changing related to the variability reported in different countries, hospitals and NICUs.

It is still unknown whether this incidence variability is due to actual genetic and/or environmental factors in the population or whether it is influenced by neonatal care strategies regardless of the ethnic origin [20].

In the most recent study period, our patients presented the pathology with a better Apgar score at 5 min, better hematocrit and platelet levels and less acidosis. They also experienced fewer fevers and more gastric residue and erythema of the abdomen. In the second period of study, specific clinical characteristics are more prevalent in our patients versus general or unspecific symptoms.

In our study, medical therapeutic strategies changed in the most recent period, with a relevant decrease in the use of prophylactic antibiotics, umbilical catheterization, transfusions and invasive mechanical ventilation consistent with a recent publication on care trends in the USA [26].

Controversy persists as to the most appropriate surgical management of NEC and especially with the time to make a surgical decision.

Among patients with NEC, those that require surgery experience the poorest outcomes and have the highest mortality [27].

Established indications for surgery in necrotizing enterocolitis are pneumoperitoneum and failure to improve or clinical deterioration with medical treatment alone. It has been proposed that infants with intestinal necrosis may benefit from surgery in the absence of one of these indications, yet the diagnosis of definitive intestinal necrosis is challenging [28].

But the reality is different; the optimal surgical plan employed is strongly influenced by clinical judgment and theoretical benefits in terms of minimizing physiologic stressors while providing definitive treatment in a timely fashion.

In the absence of pneumoperitoneum, the challenge faced by pediatric surgeons is to be able to reliably identify those infants who would benefit from surgery while minimizing the risk of the operation itself. Identifying infants with severe intestinal ischemia or necrosis due to NEC and performing a resection of the necrotic bowel would likely be beneficial and may improve outcome.

In recent years there was an international trend towards conservative management with drainage especially in critically premature infants. However, controversy about the best treatment for these critically ill patients still persists.

In our opinion, a major challenge in improving the outcome is identifying and treating infants in the early stages of the disease, not waiting until perforation or instability.

Early surgical intervention in the clinical pathway of NEC may lead to improved outcomes.

Discovering early clinical signs would facilitate early direct therapies, which could improve outcomes. In our series, in recent years surgeons are more aggressive with surgical explorations before patients experience worsening clinical status or perforation. These actions have caused an increase in surgical treatment but a decrease in overall mortality. Even though there are no statistical differences in the mortality rate between the analyzed periods, they are clinically relevant [14% vs. 5.3%].

Despite extensive research and advancement in medical and surgical treatment over the last six decades, NEC still represents a challenging condition with a high mortality rate.

The results of this study could illustrate that earlier surgical treatment of necrotizing enterocolitis in premature infants, before clinical deterioration, might improve outcomes.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Approval

This work strictly followed all ethical procedures.

Contributor´s Statement

All those designated as authors meet all criteria for authorship.

Conflict of Interest

There is no conflict of interest that could inappropriately influence our work.

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Volume 8 Issue 7 July 2019
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