NECROTISING ENTEROCOLITIS IN PRETERM INFANTS WITH GESTATIONAL AGE≤32 WEEKS IN ROMANIA: INCIDENCE AND RISK FACTORS

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Abstract

Introduction: Necrotising enterocolitis (NEC) is an acquired gastrointestinal disease associated with significant morbidity and mortality in preterm newborns. Taking into account the catastrophic development of this disease, it is necessary to focus research on prevention strategies and identify predictive risk factors for its occurrence. Aim: The aim of this study was to determine the incidence of NEC and to identify the main risk factors associated with NEC in preterm infants with gestational age(GA) ≤32 weeks admitted to neonatal intensive care units(NICUs) in Romania. Material and methods: This was a retrospective study based on the data collected in a standardised format for all preterm infants with GA ≤32 weeks born over a period of 2 years (january 2010-december 2011) and admitted to 12 tertiary-level NICUs in Romania. It was used data registered in the National Registry of Neonatal Respiratory Distress (NRNRD). A diagnosis of NEC was made based on clinical, radiological and/or histopatological evidence of stage II or III, acording to Bell's criteria. Logistic regression analysis was performed to determine the significant risk factors associated with NEC. Results: There were 1696 neonates under 32 weeks of gestation that met inclusion criteria; 1605 did not have NEC, while 91(5,3%) met criterion for NEC. Lenght of hospital stay and mortality were higher in neonates with NEC than those without NEC. Logistic regression analysis showed that smal for gestational age(SGA) and nosocomial infections were the most important risk factors for NEC. Other factors that were associated with an increased risk of NEC were bronchopulmonary displasia (BPD), use of nasal continuos positive airway pressure (CPAP), sepsis, apnea of prematurity, the lack of antenatal glucocorticoids and outborn pacients. Male gender and PDA were not statistical significantly correlated with NEC (borderline statistical significance). Conclusions: The incidence of NEC was higher in this study (5,3%). Low birth weight, nosocomial infections, BPD, CPAP, apnea and lack of antenatal glucocorticoids were associated with an increased risk of NEC in Romanian preterm infants under 32 weeks of gestation. Male gender and PDA were not statistical significantly correlated with NEC (at the limit of statistical significance).

Keywords: necrotising enterocolitis, preterm infants, risk factors

Introduction

Necrotizing enterocolitis(NEC) is an acquired inflammatory disease of the intestine, being the most common neonatal gastrointestinal emergency, that mainly affects preterm infants(1). NEC is a multifactorial disease that occurs in a high risk newborn. NEC incidence is inversely proportional to gestational age(GA), more than 90% of those affected are premature (2). With improving care at the end of the presurfactant era, the incidence of NEC declined briefly, but increased after surfanctant use became a standard of care. This reported increase is probably because of the increased survival of extremely low birth weight infants (3,4). The incidence of NEC ranged between 5%-7% and varies from country to country and between NICUs(5-8).

Because the etiology and pathogenesis of NEC are still incompletely understood, therapeutic options, morbidity and mortality were not significantly improved in the last decade of time. NEC is a major cause of mortality (between 10%-50%)(9-11) and morbidity, including recurrent sepsis, dependence on parenteral nutrition, need for surgery, survival with short bowel syndrome and neurodevelopmental delay in preterm infants.

Taking into account the catastrophic development of this disease, it is necessary to focus research on prevention strategies and identify predictive risk factors for its occurrence. The most important risk factor for NEC is prematurity and the greatest immaturity infants are at the greatest risk. Many putative risk factors have been associated with the development of NEC, both directly related to feeding practices(eg, time of feeding, use of nonhuman milk, the amount of used milk, use of fortifiants) and not related (eg, greater immaturity, smal for gestational age, respiratory distress syndrome, neonatal sepsis, mechanical ventilation, maternal pathology)(12). While many studies have identified individual risk factors related to the development of NEC, most studies include only a small number of infants with NEC, are single-institution reports, or were done in the presurfactant era. Many authors have focused on a single factor rather than exploring the additive effects of several factors(13-17).

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Characteristics	Total	NEC(n=91)	No NEC(n=1696)	p-value
Maternal factors				
Type of delivery (n,%) Cesarean Vaginal	 754(44,7%) 931(55,3%)	 41(45,6%) 49(54,4%)	 713(44,7%) 882(55,3%)	 0,874
Maternal diabetes mellitus (n,%)	21(1,2%)	0(0,0%)	21(1,2%)	0,624
Maternal hypertension (n,%)	139(8,2%)	8(8,8%)	131(8,2%)	0,831
Maternal eclampsia(n,%)	68(4,0%)	4(4,4%)	64(4,0%)	0,782
Chorioamniotitis (n,%)	75(4,4%)	4(5,5%)	71(4,4%)	0,596
Antenatal steroid prophylaxis (n,%)	507(29,9%)	18(19,8%)	489(30,5)	0,030
Premature rupture of membrane (n,%)	425(25,1%)	22(24,2%)	403(25,1%)	0,842
Neonatal factors				
Location of birth (n,%) Inpatients Outpacients	 1346(79,4%) 350(20,6%)	 63(69,2%) 28(30,8%)	 1283(79,9%) 322(20,1%)	 0,014
Sex (n,%) Male Female	 922(55,2%) 748(44,8)	 58 (64,4%) 32(35,6%)	 864(54,7%) 716(45,3%)	 0,070
GA (mean±SD,weeks)	1696	28,26±3,57	29,76±7,15	0,000
Birth weight (mean±SD)		1078,19±338,72	1346,49±518,56	0,048
APGAR score at 1 minute (mean±SD)		4,62±2,52	5,41±2,49	0,003
Growth status at birth SGA (n,%) AGA (n,%) LGA (n,%)	 576(34,0%) 1038(61,2%) 55(3,2%)	 49(53,8%) 40(44,0%) 2(2,2%)	 527(32,8%) 998(62,2%) 53(3,3%)	 0,000 0,001 0,766

Table1. Demographic and clinical characteristics of preterm infants≤32 weeks of gestation with and without NEC

Parameters	Total	NEC (n=91)	No NEC(n=1696)	p-value
Given surfactant therapy (n,%)	240(14,2%)	12(13,2%)	228(14,2%)	0.786
Use of CPAP (n,%)	999(58,9%)	67(73,6%)	932(58,1%)	0,003
Use of MV (n,%)	251(14,8%)	14(15,5%)	237(14,8%)	0,872
PDA (n,%)	372(21,9%)	27(29,7%)	345(21,5%)	0,067
Apnea (n,%)	451(26,6%)	34(37,4%)	417(26,0%)	0,017
BPD (n,%)	120(7,1%)	15(16,5%)	105(6,5%)	0,000
Sepsis (n,%)	360(21,2%)	29(31,9%)	331(20,6%)	0,011
Nosocomial infections (n,%)	91(5,4%)	16(17,6%)	75(4,7%)	0,000
IVH (n,%)	640(37,7%)	38(41,8%)	602(37,5%)	0,416
Hospital length of stay (mean±SD,days)		47,12±29,32	33,64±26,51	0,000
Outcome (n,%) Survivors/discharged Death	 1365(80,5%) 331(19,5%)	 56(61,5%) 35(38,5%)	 1309(81,6%) 296(18,4%)	 0,008

Table 2. Comparison of treatment received and outcome among preterm infants≤32 weeks of gestation with and without NEC

Variables	B	SE	Wald	p-value
SGA	0,870	0,217	16,083	0,000
Nosocomial infections	-1,471	0,300	24,079	0,000
BPD	-1,037	0,300	11,937	0,001
AGA	0,740	0,217	11,593	0,001
Use of CPAP	-0,701	0.243	8,309	0,004
Death	-1,210	0,428	8,011	0,005
Sepsis	-0,558	0,233	6,353	0,012
Outbornpacients	0,571	0,236	5,887	0,015
Apnea	-0,530	0,224	5,601	0,018
Lack of antenatal steroid prophylaxis	0,575	0,269	4,579	0,032
Borderline variables				
PDA	-0,432	0,237	3,316	0,069
MV	0,407	0,226	3,242	0,072

Table 3. Variables associated with NEC, by multiple regression analysis

We performed this study to determine the incidence of NEC among preterm infants with GA≤32 weeks and to identify the main risk factors for NEC in a large unselected Romanian cohort of preterm infants. We used a national database of preterm infants under 32 weeks of gestation to investigate the risk factors.

Material and methods

This was a retrospective, observational study based on the data of all preterm newborns with GA≤32 weeks born between January 2010-December 2011 in Romania and admitted to the NICUs of 12 tertiary-level maternity participating in the NRNRD. Participating NICUs submitted data on these infants to the NRNRD upon their discharge or death. A standardised format was used for data collection. Each infant was considered a unique case and not duplicated in the registry. The database included consecutive preterm infants for each participating center, but not all centers contributed neonates for all 2 years (9 centers in 2010 and another 3 centers in 2011). Neonates who died in the first day of life, those under 23 weeks of gestation and those with congenital anomalies were excluded from the study.

The diagnosis of NEC was made based on the presence of clinical, radiological and/or histopathological evidence that fulfilled the stage II or III of Bell's criteria(18).

The potential risk factors considered were classified into 4 cathegory:

• neonatal factors: location of birth, gestational age, birth weight, sex, growth status at birth: being smal for gestational age (SGA, birth weith<10th percentile for respective gestational age), appropriate for gestational age (AGA, birth weith between 10th-90th percentile for respective gestational age), large for gestational age (LGA, birth weith >90th percentile for respective gestational age)(19,20), APGAR score at 1 minute

• maternal factors: maternal insulin-dependent diabetus mellitus, maternal hypertension, maternal eclampsia, chorioamniotits, antenatal steroid prophylaxis, premature rupture of membrane(over 18 hours), type of delivery

• factors related with resuscitation: surfactant therapy, use of nasal continuos positive airway pressure (CPAP), need for mechanical ventilation(MV)

• newborn diseases: presence of patent ductus arteriosus(PDA), intraventricular haemorrhage(IVH), apnea of prematurity, bronchopulmonary disease (BPD), sepsis, nosocomial infections, hospital length of stay, outcome (discharge, death).

The diagnosis of PDA was made based on the presence of a continuous heart murmur in the left second, intercostal space, hyperdynamic precordium, wide pulse pressure, bounding pulses and an increased pulmonary vasculature or cardiomegaly in the cest radiograph, or echocardiografic evidence of PDA. IVH was defined as the presence of haemorrhage in the intraventricular, periventricular or subependymal regions of the lateral ventricles of the brain as detected by cranial ultrasonography. Preterm apnea was defined as respiratory pause lasting 20 seconds or less, but accompanied by cyanosis or bradycardia. BPD was defined as needing oxygen therapy for more than 28 days and at 36 weeks of gestation. Sepsis was defined as the presence of clinical evidence of sepsis with positive microbiological culture in aseptically collected blood or cerebrospinal fluid specimens. Nosocomial infection was defined as a systemic infection manifested after the first 72 hours of life, caused by an infection transmitted vertically by existing microorganisms in the maternal cervico-vaginal canal or horizontally by contamination of the external environment.

Statistical analysis was performed using SPSS Version 17 Program. Results are expressed as mean± SD. Univariate analysis was used to compare the variables for the outcome groups of interest (pacients with NEC vs. patients without NEC). Comparisons were unpaired and all tests of significance were 2-tailed. Continuous variables were compared using Student's t test for normally

distributed variables. All p values< 0.05 were considered statistically significant. Chi-square test (or Fisher's exact test for variables with expected values <5) was used for univariate analysis of categorical variables. To establish the predictors for NEC it was used the binomial logistic regression, Wald model.

Results

There were 1696 neonates under 32 weeks of gestation that met inclusion criteria; 1605(94,7%) did not have NEC, while 91(5,3%) met criterion for NEC. From all 1696 preterm infants, 500(29,48%) were of gestation ≤28 weeks. A majority (79,4%) of the preterm infants were born to inpatients.

Univariate analysis showed no significant difference in the maternal factors between preterm infants with and without NEC, except for the use of antenatal steroid prophylaxis (Table 1). The proportion of mothers receiving antenatal steroids was significantly lower among childrens with NEC. The infants with NEC, compared with those without NEC, were of significantly lower birth weight and gestational age. Regarding neonatal factors, univariate analysis showed significant difference between infants with and without NEC for the following characteristics: GA, birth weight, SGA, AGA, APGAR score and outpatients. This factors were associated with an increased risk for NEC. Male gender and PDA were not statistical significantly correlated with NEC (borderline statistical significance).

Discussions

We conducted a retrospective, observational study to find the incidence and the risk factors for NEC in preterm infants≤32weeks of gestation. Our study population included preterm infants from 12 tertiary-level NICUs in Romania. NEC was defined based on the presence of clinical, radiological and/or histopathological evidence that fulfilled the stage II or III of Bell's criteria(17).

In our study, the incidence of NEC among preterm infants ≤32 weeks was 5,3%, much higher than that reported in other studies (Italy-3,1%, United States-2,6%, Australia-3,8%)(5,12,21), but lower than that reported in one big Malaysian study (6,2%)(22). Incidence of NEC varies significantly from country to country and between NICUs. Criteria for preterms inclusion in the studies may differ from one center to another. A study from United States had shown that NEC occurs in approximately 10% of infants born with a weight lass than 1500g with a large variation ranging from 2% to 22%, depending on the centre of inquiri(23). Another recent surveys on a large samples of VLBWIs in North America have shown an incidence ranging from 6,6% to 7,1%(7,8,11).

Similar to the findings of Canadian and Australian studies(8,12), the data from our study showed that low gestational age was a significant risk factor associated with NEC. This was different from the findings of Guthrie, Kosloske and Holman et al(3,21,24), which reported that decreasing birth weight was the main risk factor for NEC.

We also find that the use of antenatal glucocorticoids decrease the incidence of NEC, similar to the vast majority of previous studies(25, 25). A few studies found the opposite relationship (i.e., antenatal glucocorticoids increase the incidence of NEC)(21,27,28). The hypothesize could be that the protective effect of antenatal glucocorticoids might be birth-weight-specific and the number of doses may influence the effects. Repetitive doses of glucocorticoids may have different morphologic effects upon gastrointestinal development when compared to a single dose.

Several risk factors for the development of NEC identified by other studies such as apnea, BPD, sepsis, nosocomial infections, were also found to be associated with NEC in our study(22,29,30).

Use of CPAP was associted with the developing of NEC in this study, being different from other reports(31).

Contrary to other studies(5,32), PDA was not a significant independent risk factor associated with NEC in our study. Probably not all childrens in our study were diagnosed with PDA due to several factors: impossibility of ultrasound PDA diagnosis because of lack of cardiologists in many centers, there is no single diagnostic protocol in the country and also the time of diagnosis is very important.

The outborn pacients had in our study the risk for developing NEC, similar to another reports(33). The factors that could be associated with the higher incidence of unfavorable outcomes among outborn infants include ineffectiveness of stabilization procedures before or during transport, delays in commencing assisted ventilation or use of surfactant, risk of infections and delays in transport(34). In addition, transport itself is a stressor that can adversely affect this babys(35). There are many possible factors for the improved outcomes of preterm infants at tertiary centers, including availability of laboratory, radiologic, and specialist medical support, and more adequate staffing and equipment to provide optimal care in the delivery room and NICUs(34).

Our data confirm previous reports that NEC is an important neonatal problem associated with significant morbidity and mortality(3,4). In this study the mortality rate of infants with NEC was significant(38,5%), similar to the findings of other studies(3,7,8,23,24), and the newborns with NEC also had a longer hospital length of stay.

Conclusions

The incidence of NEC among preterm infants ≤32 weeks was higher(5,3%) in our study. Low birth weight, SGA, nosocomial infections, BPD, CPAP, apnea of prematurity and lack of antenatal glucocorticoids were associated with an increased risk of NEC in Romanian preterm infants under 32 weeks of gestation. Male gender and PDA were not statistical significantly correlated with NEC (borderline statistical significance).

In summary, NEC is still a common problem affecting preterm infants, with the incidence and mortality remained unchanged in recent years. A number of modifiable risk factors associated with NEC have been identified and it is possible that such factors might help us to plan optimal preventive strategies to reduce the incidence of NEC in preterm babys.

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