CONTRIBUTING FACTORS FOR DEVELOPMENT OF NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS IN THE NEONATAL INTENSIVE CARE UNIT

Zlatan Zvizdic¹, Suada Heljic², Nusret Popovic¹, Jasmina Alajbegovic-Halimic³, Emir Milisic¹, Asmir Jonuzi

¹Clinic of Pediatric Surgery, University Clinical Center, Sarajevo, Sarajevo, Bosnia and Herzegovina
²Pediatric Clinic, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina
³Eye Clinic, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina

Corresponding author: Zlatan Zvizdic, MD; PhD; Clinic of Pediatric Surgery, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina. Phone: +387 61 194 924; E-mail:zlatan.zvizdic@mf.unsa.ba

ABSTRACT

Background: Necrotizing enterocolitis is a serious condition that affects mostly preterm infants, with high mortality rate. Aim: to estimate the influence of potentially contributing factors of this multifactorial disease. Methods: The study group included 51 necrotizing enterocolitis infants who were less than 37 week gestation who were hospitalized in NICU during a five year period. The control group consisted of 71 patients with approximately the same gestational age and birth weight. Average gestational age in the study group was 30.2 weeks (SD 3.7), average birth weight 1502g (SD 781.5). Average postnatal age in the time of the presenting NEC was 18.2 days (SD 12.8). Results: Logistic regression estimates the influence of risk factors, which in our study related to the treatment of preterm infants on the likelihood of NEC development. Our regression model consisted of seven independent variables (nosocomial infections, mechanical ventilation, nasal continuous positive pressure, morphine, inotropes, blood transfusions, and H2 blockers), which were shown to have a statistically significant impact, X² (7, n=1222) = 49.522, p<0.0001; two independent variables (nosocomial infection and H2 blockers use) were statistically significant. Preterm infants with nosocomial infection had a three times greater chance of developing NEC, and infants who received H2 blockers had a 1.5 higher risk.

Conclusions: Underlying pathology of very low birth weight infants and their treatment in NICU contribute to NEC development. Identifying risk factors can be crucial for the early diagnosis and outcome of disease. Awareness of risk factors should influence changes in practice to reduce the risk of NEC.

Keywords: necrotizing enterocolitis, preterm infants, contributing factors.
(12). However, understanding of possibly harmful effects of any management alternative is crucial in reducing the morbidity rate of and disease, including NEC; a disease in which therapeutic interventions include: red blood cell transfusions, long term antibiotic therapy for nosocomial infections, mechanical ventilation, infusion of morphine to relieve pain, reduce the stress response, and of medications including methylxanthines and H2 blockers.

2. PATIENTS AND METHODS

This retrospective study was performed on all NEC preterm infants (<37 weeks gestation at birth) admitted in the NICU of our institution over a period of five years, from 2008 to 2012. Gestational age was routinely determined from the last menstrual period, early ultrasound investigation or using the New Ballard score, and recorded as completed weeks (13).

Diagnosis of NEC was made based on the presence of clinical, radiological and/or histopathological evidence that fulfilled the criteria of Bell’s (14) as well as Walsh’s modification of these criteria (15).

Definition of nosocomial infection (NI): NI infection is defined as an infection that occurs after 48 hours of hospitalization, resulting in a positive blood, cerebrospinal fluid (CSF), or urine culture with clinical manifestations such as hospital-acquired bloodstream infections, nosocomial pneumonia, sepsis, urinary tract infection and meningitis.

Medical NEC was defined as the presence of radiological signs of intestinal pneumatosis and when the disease is treated with antibiotics for more than two days. Surgical NEC was defined as any surgical treatment. The infants’ medical records were reviewed daily for medical course information until hospital discharge or death of infant. A standardized format was used for data collection.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA). The number of infants with each investigated factors (nosocomial infections, MV, NCPAP, morphine sulfate, inotropes, RBC transfusions, H2 blockers) was compared between groups with and without NEC. Categorical variables were compared using the χ2 test. The means of continuous variables were compared using Student’s t test, and the data are presented as mean (SD). The influence of relevant confounding variables, identified by univariate analysis, was assessed using multivariate logistic regression analysis. Confidence intervals presented for odds ratios are adjusted for the clustering of infants within participating nurseries. Statistical level of 95% (p<0.05) was considered as significant for all performed tests.

3. RESULTS

During the study period, 830 preterm infants were admitted in the NICU; 51 (6.1%) got NEC. Control group consisted of 71 randomly selected preterm infants that were not significantly different in BW and GA from premature infants with NEC. In the group of patients with NEC, based on the diagnostic criteria (12, 13), presence of the medical NEC established in 30 patients (58.8%) while the surgical NEC found in 21 patients (41.2%).

Average gestational age of preterm infants with NEC was 30.2 GW (SD 3.7), average birth weight 1502.75 g (SD 781.5). Postnatal age in time of appearance of NEC was 18.2 days (SD 12.8) (2-57 days); 49% infants were older than 2 weeks. In one patient NEC developed before starting of enteral feeding. The most common gastrointestinal symptoms in the study group were: abdominal distension in 89% cases, macroscopic or microscopic blood in the stool in 56.9% and increasing gastric residuum in 46% cases.

Table 2. Risk factors related to the hospitalization and treatment of VLBW infants

<table>
<thead>
<tr>
<th></th>
<th>NEC (N=51)</th>
<th>Control (N=71)</th>
<th>NEC vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial infections</td>
<td>29/51 (56.9%)</td>
<td>17/71 (24.6%)</td>
<td>p=0.004</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>37/51 (72.5%)</td>
<td>14/71 (19.7%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Inotropes</td>
<td>33/51 (64.7%)</td>
<td>9/71 (12.7%)</td>
<td>p=0.0031</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>43/51 (84.3%)</td>
<td>22/71 (31.0%)</td>
<td>p=0.0158</td>
</tr>
<tr>
<td>NCPAP</td>
<td>25/51 (50.0%)</td>
<td>39/71 (55.0%)</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>H2 blockers</td>
<td>20/51 (39.2%)</td>
<td>6/71 (8.5%)</td>
<td>p=0.0005</td>
</tr>
<tr>
<td>Transfusions RBC</td>
<td>31/51 (60.8%)</td>
<td>21/71 (29.6%)</td>
<td>p=0.0031</td>
</tr>
</tbody>
</table>

Table 3. Model for logistic regression - Factors of treatments

<table>
<thead>
<tr>
<th>No</th>
<th>Factors</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nosocomial infections</td>
<td>0.033</td>
<td>3.169</td>
<td>1.0993 – 10.086</td>
<td>2.955</td>
<td>0.0031</td>
</tr>
<tr>
<td>2</td>
<td>MV</td>
<td>0.1017</td>
<td>1.1848</td>
<td>0.9671 – 1.4515</td>
<td>1.917</td>
<td>0.054</td>
</tr>
<tr>
<td>3</td>
<td>CPAP</td>
<td>0.3133</td>
<td>0.9117</td>
<td>0.7618 – 1.0911</td>
<td>1.017</td>
<td>0.310</td>
</tr>
<tr>
<td>4</td>
<td>Morphine sulfate</td>
<td>0.0823</td>
<td>1.8500</td>
<td>0.9242 – 3.7031</td>
<td>2.955</td>
<td>0.0031</td>
</tr>
<tr>
<td>5</td>
<td>Inotropes</td>
<td>0.8442</td>
<td>0.9117</td>
<td>0.7618 – 1.0911</td>
<td>0.017</td>
<td>0.984</td>
</tr>
<tr>
<td>6</td>
<td>RBC transfusions</td>
<td>0.2634</td>
<td>0.6474</td>
<td>0.3022 – 1.3870</td>
<td>0.017</td>
<td>0.984</td>
</tr>
<tr>
<td>7</td>
<td>H2 blockers</td>
<td>0.0269</td>
<td>1.5503</td>
<td>1.0514 – 2.2861</td>
<td>1.017</td>
<td>0.310</td>
</tr>
</tbody>
</table>
of days on NCPAP in NEC group (Md=5 n=25) and control group (Md=3 n=39). U=313.50, z=2.413; p=0.0158.
20/51 (39.2%) infants in NEC group received H₂ blockers (an average of 2.2 days), in control group 6/71 (8.5%) (an average of 0.25 days), which is statistically significant \( \chi^2 (1, n=122) = 14.967, p=0.0001 \).

There was statistical difference in RBC transfusions in NEC group (Mean 1.53 n=31) and control (mean 0.55 n=21). \( \chi^2 (1, n=122) = 10.578, p=0.0011 \).

Logistic regression is done to estimate the influence of factors related to treatment of sick infants on possibility to develop NEC. Model consists of 7 independent variables (nosocomial infections, MV, NCPAP, morphine sulfate, inotropes, RBC transfusions, \( H_2 \) blockers).

Whole model with all predictors was statistically significant, \( \chi^2 (7, n=122) = 49.522, p<0.0001 \), which indicates that model can recognize infants who may develop NEC later. Two independent variables (nosocomial infections and \( H_2 \) blockers use gave statistically significant contribution to the model. Logistic regression analysis showed that there was a statistically significant association in the number of nosocomial infections prior NEC diagnosis with the development of NEC (\( p<0.05 \)). Based on the result of logistic regression analysis, it can be concluded that each additional infection increased the odds of developing NEC by 3 times, and use of \( H_2 \) blockers 1.5 times.

4. DISCUSSION

Incidence of NEC in our study was 6.1\% (51/830) consequently admitted preterm infants in NICU. The incidence generally varies from neonatal units, regions and countries, as can be determined by different definition of NEC (2). Although in clinical practices predominant definition is suggested by Bell et al. (14) and modified by Walsh et al. (15), in literature still exists mismatch of uniform recognition and classification of suspected NEC in VLBW and ELBW infants (2). To determine potential risk factors and predictors for NEC development (clinical, radiological and laboratory), we tried to achieve the most homogeneous study group of infants with NEC and control group; there was no statistical difference between groups in gestational age and birth weight. Average gestational age in patients with NEC was 29.96 ± 3.67, BW 1461.08 ± 781.47 g, which is in agreement with similar studies (16, 17).

Investigations related to nosocomial infection and developing of NEC indicate that increasing number of infections before clinical manifestation is associated with increasing risk for NEC (18). Although there is no exact identification of reasons for this kind of connection in the literature, it is assumed that can be in relationship with duration of parenteral nutrition. Parenteral nutrition has been shown to have immunosuppressive effect with decreasing the grade of phagocytosis and neutralization coagulase negative staphylococci. (19). Results of our study showed that the number of nosocomial infections before clinical manifestation of NEC was significantly higher than in control group (\( p=0.0004 \)).

Respiratory insufficiency of preterm infants is relatively frequent, including inability to maintain normal gas exchange. That is why respiratory support routinely carried out especially in VLBW and ELBW infants, using mechanical ventilation (MV) or continuous positive pressure ventilation through nasal prongs (NCPAP). NCPAP as non-invasive procedure used today as important alternative, has reducing the incidence of chronic lung disease, retinopathy, intraventricular bleeding and incidence of neurodevelopmental disorders. Meyer et al. (20) concluded that VLBW and modality of respiratory support can be a risk factor for NEC development, so it can serve as a predictor for development and severity of the disease. Possible explanations can be in cognition that VLBW infants have higher need for respiratory support before gastrointestinal symptoms, compared to infants of the same birth weight without NEC. Dolgin et al. (21) in their study found that preterm infants with surgical NEC have higher need for respiratory support–MV or NCPAP compared to preterm infants with medical NEC. Results of our study showed that duration of mechanical ventilation in days prior gastrointestinal symptoms in infants with NEC was statistically significantly higher compared to control group (\( p=0.0031 \)).

Although anemia of prematurity is the usual in this group of age, caused by incomplete placent transport of Fe, leak of complete fetal erythropoiesis, iatrogenic blood loss, low level of erythropoietin in plasma and increasing needs due to fast body growth, frequent red blood cell transfusions were common clinical practices in NICUs. This practice is now revised and becomes more restrictive. Reasons for this are in the cognition of relationship between RBC, acute intestinal injury and serious gastrointestinal reaction, especially in ELBW and extremely preterm infants (22, 23).

However, mechanism of which RBC causes injury on GI tract of preterm infants is not researched enough. Simmonds et al. (24) offered some explanations as decreased capacity of nitric oxide storage in packed RBC, excessive intestinal immunological response and alteration of mesenteries blood flow after RBC transfusion result in intestinal hypoxia and intestinal mucosal injury. All of that suggest that RBC transfusions can cause alteration gastrointestinal microcirculation in the supply of oxygen during this vulnerable period and significantly contribute to NEC developing.

Our study showed that preterm infants with NEC had significantly more RBC transfusions before clinical signs of NEC compared to control group (\( p=0.0005 \)). This result is in concordance with similar studies that determined positive correlation between RBC transfusions and appearance of NEC (22, 23).

Morphine sulfate is used to be common praxis in ventilated infants in NICUs due better of synchronization with ventilator, pain relief and reduction of stress response. Its use has been decreasing steadily because of its adverse effects including hypotension, bradycardia, delay in beginning of enteral feeding and reduction of gastrointestinal motility. (25). General acceptability of morphine administration in preterm infants in era of non-invasive ventilation and high antenatal steroid use is now questionable (25).

Hällström et al. (26) first noticed that duration of morphine sulfate administration have significant influence on NEC development. Additional explanation is that reduction of gastrointestinal motility allows prolonged contact GI bacteria with feeding substrates and gut wall, bacterial translocation with increasing possibility for development.
of disease. Our results showed that infants with NEC had statistically significant higher number of days of morphine administration compared to control group (p=0.0001).

Use of inotropes (dubutamine, dopamine) is common in presence of shock or hypotension, to achieve cardiovascular stabilization. Action of dubutamine is based on its action on β receptors, resulting in improving of heart contractibility, vasodilatation and mild tachycardia. Bedside this action, Hentschel et al. (27) using doppler ultrasonography on mesenteric artery, determined increased intestinal perfusion and concluded that is no influence on NEC development, although pathophysiological mechanism of this connections still is not clear.

Use of inhibitors gastric acid secretion can cause insufficient elimination of ingested pathogens and increase risk of nosocomial infections, due to alkalization of gastric content which normally presents the main non-immune mechanism of defense against infection (28). HistaminH2 receptors blockers and proton pump inhibitors (ranitidin, famotin, and cimetidin) increase the risk of infection and NEC in neonatal period (28). Administration of those medicaments reduces proteolytic activity of gastric secretion, allowing gastric colonization with gram negative strains, and consecutive pneumonia and gram negative sepsis. (28) Use of Histamine H2 blockers in NICUs is empiric, especially in infants with proven GI bleeding and GI reflux. Although in these cases administration can protect mucosa from extensive production of gastric acid and prevent stress ulcers, in the same time it can neutralize natural defense against overgrowth propagation (28). In study in Terin et al (28) in infants receiving H2 blockers number of infection was 4 times higher. Our investigation showed significant association between H2 blockers and NEC development (p=0.0001).

Logistic regression of 7 independent variables (nosocomial infections, MV, NCPAP, morphine sulfate, inotropes, RBC transfusions, H2 blockers) was statistically significant, \( \chi^2 (7; n=122) = 49.522, p=0.0001, \) which indicates that model can recognize infants who may develop NEC later. Two independent variables (nosocomial infections and H2 blockers use gave statistically significant attribution to the model.

Based on the result of logistic regression analysis, it can be concluded that each additional infection increased the odds of developing NEC by 3 times, and administration of H2 blockers 1.5 times.

5. CONCLUSION

Underlying pathology of VLBW infants and their treatment in NICU contribute to NEC development. Identifying risk factors can be crucial for the early diagnosis and outcome of disease. Awareness of those risk factors changes practices to reduce the risk of NEC.

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- Conflict of interest: none declared.

REFERENCES


