

Risk Factors, Prevention and Treatment of Neonatal Necrotizing Enterocolitis in 70 Newborn Infants

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ABSTRACT

Objective: To determine the risk factors in neonatal necrotizing enterocolitis (NEC) and provide options for the prevention and treatment of NEC.

Methods: Clinical information of 70 newborn infants with NEC, admitted to our hospital between January 2004 and April 2012, were reviewed and analyzed, including clinical characteristics, maternal factors during perinatal period, newborn factors, feeding history, concomitant diseases, antibiotic treatment and prognosis.

Results: The time of onset was 1-28 days (with median of 7 days) after birth and 58 cases (82.9%) suffered from NEC within 14 days of birth. Staging: 21 cases (30%) were stage I (suspected as NEC), 21 cases (30%) were stage II (confirmed as NEC) and 28 cases (40%) were in stage III (severe NEC). Maternal factors during perinatal period, newborn factors, feeding, concomitant diseases and administration of antibiotics, all played a role in the treatment of NEC.

Conclusion: NEC is associated with premature, low birth weight, infection, improper feeding, delay in meconium excretion, accompanied by severe anoxic and ischemic disease and improper antibiotic treatment.

Keywords: Necrotizing enterocolitis, newborn infants, prevention, risk factors, treatment

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INTRODUCTION

Necrotizing enterocolitis (NEC) is considered as the most serious gastrointestinal disease in neonatal intensive care unit (NICU), which greatly threatens the life of newborn babies (1-2). It had been reported in literatures that the morbidity of NEC was 0.1-0.3%, which could be up to 7-10% in extremely low birth weight infants. So far, neither the true incidence nor the pathogenesis of NEC is completely understood. NEC gained notoriety in the 1960s following epidemic of cases at the Babies hospital in New York city between 1955 and 1966 (3). Since then, there have been several studies done looking at different aspects of NEC and their numbers have consistently increased over the years. However, controversy still exists as to the appropriate treatment of neonates with NEC. The development of necrotizing enterocolitis also varies according to geographical and ethnic distribution, with lower frequencies in Japan, Switzerland, and Austria, and higher frequencies in Northern America, the UK and Ireland (4-5). Currently the diagnosis of NEC is made by clinical and radiological signs according to modified Bell's staging criteria (6). Relying solely on clinical symptoms could result in omission of diagnosis since systemic and abdominal signs are non-specific in newborns. Similarly, radiological signs also lack sufficient discriminative power due to time delay (7). Accurate and timely diagnosis of NEC could reduce morbidity while improving quality of life and reducing cost of care. Therefore, we carried out retrospective investigation in the 70 cases diagnosed with NEC who were admitted by our hospital from Jan. 2004 to Apr. 2012, so as to analyze the risk factors and clinical characteristics of the disease and thus provide certain reference data for NEC prevention and treatment.

MATERIALS AND METHODS

Among the newborn infants admitted into the hospital between January 2004 to April 2012, 70 cases clinically diagnosed with necrotizing enterocolitis were selected, and clinical analyses were performed on relevant factors, which can be seen below.

Diagnostic criteria: In accordance with *Practice of Neonatology* (4th edition) and amended Bell-NEC grading criteria, clinical diagnosis and NEC stages were identified.

Observation of relevant factors: (1) clinical characteristics: onset age in days and staging of disease; (2) maternal factors during perinatal period: a) infection: premature rupture of fetal membranes and antenatal infection (including antenatal fever, respiratory tract infection and erythritis); b) abnormal placenta and umbilical cord: placental abruption, placenta previa, cord around neck and paramorphia of placenta and umbilical cord; c) hypertension during pregnancy: pregnancy-induced hypertension and chronic hypertension; d) history of anoxia during perinatal period: intrauterine hypoxia and anoxia after birth; e) mode of delivery; f) history of antenatal hormone therapy; (3) newborn infant factors: a) whether or not neonate was a twin; b) gestational age and birth weight; c) time of meconium excretion: delay and prolongation of meconium excretion; (4) feeding factors: a) time of onset of feeding; b) type of feeding (breast, formula or other); c) maximum premorbid feeding volume and feeding rate; (5) concomitant disease: anemia, septicemia, intracranial hemorrhage, patent ductus arteriosus, atrial septal defect, patent foramen ovale, respiratory distress syndrome, hypoglycemia and congenital megacolon; (6) history of antibiotic treatment: antibiotic administration and the duration of administration; (7) prognosis: a) complication: intestinal perforation and peritonitis; b) final therapeutic outcome.

RESULTS

Clinical characteristics: The time of onset ranged from 1-28 days after birth (with a median of 7 days). 58 cases developed NEC within 14 days, which made up 82.9% of the total. There were 21 cases (30%) diagnosed as stage I (suspected as NEC), 21 cases (30%) stage II (diagnosed with NEC) and 28 cases (40%) stage III (diagnosed with severe NEC).

Pregnancy factors in the perinatal period are specified in table 1. As to the mode of delivery, there were 30 cases (42.9%) that were natural delivery and 40 cases (57.1%) that had a cesarean. Antenatal hormone was administered in 9 (19.1%) of the cases.

Infant factors

(1) There were 10 infants (14.3%) that were a pair of twins, with 2 as a pair of males and the other 8 infected cases were a pairs of one male and one female, in good health.

(2) Gestational age and birth weight: Among the NEC cases in the retrospective investigation, the gestational age ranged from 26 weeks to 42 weeks, with an average of 34.5 ± 4.3 weeks, which is shown in table 2. The minimum birth weight was 770g, and the maximum was 4025g, with an average of 2120 ± 930 g, and the distribution of birth weight is shown in table 3.

(3) Excretion of meconium: There were 37 cases with delayed meconium excretion, (68.5%) among the identified cases with meconium medical history (16 cases did not have a clear history of meconium excretion)

Feeding history: The time of onset of feeding is shown in Table 4. There were 6 cases (8.6%) considered as not feeding prior to NEC onset. The milk product categories used for premorbid gastrointestinal feeding are shown in Table 5. The maximum feeding volume for the premorbid infants ranged from 1.6-180.8mL/Kg/d with a median of 46.4 mL/Kg/d and 13 cases (18.6%) had a rapid increase [>20 mL/Kg/d] in feeding and one case, which was fed at home had an

increase in feeding was up to 51.7 mL/Kg/d.

Concomitant disease: Among the 70 NEC cases, 60 cases (85.7%) were identified as having related concomitant diseases, which are specified in Table 6. Of the 39 cases with septicemia, 17 cases (43.6%) demonstrated a positive blood culture and the pathogenic strains were *Escherichia coli* in 6 (33.3%), *Klebsiella* in 4 (22.2%, including 2 strains of *Klebsiella pneumoniae* and *Klebsiella oxytoca* respectively), 2 cases of *baumanii* (11.1%), *candida glabrata* in 2 (11.1%) and 1 each of *enterococcus faecalis*, *pseudomonas aeruginosa*, *staphylococcus haemolyticus*, *candida albicans* (5.6%).

History of antibiotics administration: there were 33 cases (47.1%) where antibiotics were administered before NEC. Among 27 cases were clearly diagnosed as infection and 6 cases (14%) received antibiotics for prevention with no clear history of infection. The duration of premorbid administration of antibiotics ranged from from 1-14 days (median of 5 days).

Prognosis: There were 11 cases (15.7%) with concomitant intestinal perforation and 13 cases (18.6%) with peritonitis. Data showed that 43 cases (61.4%) were cured, 10 cases (14.3%) discontinued treatment and 17 cases (24.3%) died.

DISCUSSION

Necrotizing enterocolitis (NEC) is considered to be the most serious gastrointestinal disease among newborn infants, which can occur at any time during the entire neonatal period but is most common from 2 to 12 days after birth. Of the cases chosen in this study, the time of onset ranged from 1-28 days (with a median of 7 days) and 82.9% cases had an NEC attack within 14 days after birth. The reason for NEC episodes occurring early in the neonatal period is due to the

adaptation from utero to extra uterine environment. Premature infants have poor adaptive capacity and are easily influenced by external environment such as temperature, feeding and other factors that influence respiratory and circulatory function. 7-14 days after birth is a period of weight recovery and with an increase in feeding volume which could lead to feeding intolerance. Premature infants are also easily susceptible to various complications, such as infection, respiratory distress syndrome (RDS), anemia, patent ductus arteriosus and intracranial hemorrhage. These factors could affect circulation resulting in intestinal ischemia and anoxia, thus accelerating the onset of NEC. As to term infants, the time of disease onset is variable. In our study among the 23 term cases, 7 (30.4%) had disease onset within 3 days. The cause was intrauterine infection, which resulted in serious infection in the infants with hemodynamic disorder of the intestinal wall resulting in NEC. Another 7 (30.4%) had disease onset after a long period following birth and in combination with congenital megacolon, mainly due to delay in meconium excretion and faeces stagnating in the intestinal tract, resulting in circulatory disturbance. Endogenous infection along with excretory function disorder resulted in NEC.

The onset of NEC might also be related to the factors in perinatal period such as pregnancy-induced hypertension. In this study we found that the factors in the perinatal period could induce anoxia in infants thus resulting in developmental immaturity of gastrointestinal tract, becoming the pathological basis of NEC. In our study premature infants were 67.1% and low birth weight infants made up 65.7% of the cases, further indicating that these factors could predispose NEC. Infants infected during perinatal period made up 41.4% of the cases which could lead to premature birth and was considered as a high risk factor of NEC.

The relationship between the time of onset of feeding, the maximum premorbid feeding volume and feeding rate, and the onset of NEC has not been studied in detail up to now. In this

study, 91.4% cases had onset of NEC after feeding and infants fed 4 days after birth made up 90% of the cases. There was a significant difference in feeding volume before the onset of NEC and the infants with a rapid increase (>20 mL/Kg/d) made up 18.6% of the cases. Since the subjects were admitted to neonatal intensive care unit (NICU), and were in a morbid state, early feeding under pathological conditions and intolerance to feeding could lead to NEC. As to the mode of feeding, it was found that the occurrence of NEC in infants fed with formula milk powder was higher than those that were breast fed. The reason could be that breast milk promotes maturation of gastrointestinal tract, offers immuno-protection and its osmotic pressure is lower than formula milk powder.

In addition, we also found that 68.5% infants had delay in meconium excretion due to various factors including, developmental immaturity of gastrointestinal tract in premature infants comorbidities affecting gastrointestinal function and congenital intestinal deformity,. These could all induce poor intestinal tract movement resulting in retention of food, which could provide nutrition for bacterial growth resulting in endogenous infection.

We also found that 85.7% of the infants had comorbidities, the most common among which were anemia (68.6%) and septicemia (55.7%). It has been universally acknowledged that infection and inflammatory response are risk factors of NEC (8). In this study the pathogenic bacteria in septicemia were mainly *Escherichia coli* and *Klebsiella*, which are opportunistic pathogens. These comorbidities resulted from immunodeficiency as well as other intestinal problems in infants.

Bury et al. found that preventative application of antibiotics could reduce the incidence of NEC, in a Meta-analysis, in 2001 (9-12). However, there are studies showing that the application of antibiotics for $>$ than 5 days would increase the risk of NEC (10). In our study, 33 cases (47.1%)

received antibiotics before onset of the disease. 6 of these infants (14%) received preventative antibiotics for 1-14 days, with no history of infection. Therefore, the administration of antibiotics could be related to the onset of NEC. Administration of broad-spectrum antibiotics might result in alteration of intestinal flora in infants, particularly those that could not be fed, affecting the establishment of normal intestinal flora resulting in NEC.

Interestingly, in this study 43 infants were cured, while 17 died and the rest discontinued treatment. Nearly 40% of the cases were stage III (severe NEC) which is difficult to cure. Therefore, NEC should be diagnosed in the early stage and requires timely treatment. Specific therapy for NEC is not available at present and constitutes a multi-faceted approach including: a) fasting, gastrointestinal decompression and intravenous nutrition; b) infection control; c) supportive and symptomatic treatments such as respiration and circulation support, maintaining fluid and electrolyte balance, as well as combating anemia, shock, DIC and multiple organ insufficiency; d) surgical treatment: infants with intestinal perforation grouped under absolute surgical indication; those with oliguria, hypotension, metabolic acidosis, rigidity of intestinal loop grouped under relative surgical indication and those with surgical indications without any consensus included portal vein pneumatosis, enclosed mass in right lower quadrant and red and swollen praeabdomen wall (11); e) N-acetylcysteine and intestinal trefoil factor could decrease the degree of intestinal impairment in NEC animal model (13).

Aggravation of NEC could result in a more complex therapeutic regimen, while early diagnosis could reduce the complexity of treatment. Therefore, early detection is of great importance in the treatment and prognosis of NEC. At present, there are several studies looking at the use of ultrasound in NEC diagnosis and illness monitoring. Ultrasound showing portal vein pneumatosis could be used as a differentiator in the diagnosis of the NEC and other digestive

system diseases in newborn infants (14). Abdominal color Doppler ultrasound is of unique diagnostic value in identifying bowel necrosis at an early stage so as to improve NEC staging and evaluate the prognosis (15). It is also superior to plain X-ray in revealing free liquid in enterocoli and portal vein pneumatosis, which is of great diagnosis value in NEC-induced early intestinal perforation. In the past, the consensus for the diagnosis of stage III NEC was using abdominal X-ray, successively, at 6-8 hour intervals to observe pneumo-peritoneum and for timely identification of intestinal perforation. The dynamic observation using ultrasound improves the chances of early discovery of intestinal perforation and provides effective reference for surgery. It also prevents the damage of ionizing radiation in newborn infants. Therefore, ultrasound is of great importance in the diagnosis, therapy and monitoring of NEC (15).

A lack of specific therapy for NEC stresses the importance of its prevention. The key to the prevention of NEC relies on improving intestinal tract circulation. This helps to avoid intestinal tract ischemia and anoxia, prevent infection, establish normal intestinal flora and, maintain normal defecation so as to prevent the onset of NEC. Prevention of NEC in premature infants should emphasize on a) health care in the perinatal period, including timely treatment of ischemia and anoxia or other infectious diseases in pregnant woman; b) prevention or treatment of diseases that induce NEC, such as anemia, septicemia, intracranial hemorrhage, patent ductus arteriosus, atrial septal defect, respiratory distress syndrome and hypoglycemia; c) breast feeding: the time of onset, feeding volume and feeding speed should be decided by feeding intolerance and the fasting time should be shortened if necessary.

In 2012, it was reported that median dose of erythrocin could treat intolerance of feeding in premature infants and reduce the risk of the onset of NEC (16); d) ensuring bowel evacuation, by belly message and artificial bowel movement; e) prevention of infection: reducing iatrogenic

blood sampling times and strict aseptic technique to avoid in-hospital infection; f) controlling liquid volume; g) reinforcing management of newborn infants, including the management of body temperature, respiration, circulation, nutrition and monitoring of nervous system and hemodynamics; h) avoiding the usage of preventative antibiotics, but selecting narrow-spectrum antibiotics in the treatment of infectious diseases, while strictly managing the duration and dosage medication.

In mature infants, NEC is secondary to infection and developmental malformation of the digestive system, such as congenital megacolon. Therefore, besides the above preventive measures, artificial bowel movement and cleansing enema should be used for those who cannot defecate normally, so as to prevent endogenous infection.

In recent years, the use of probiotics to prevent the onset of NEC has been advocated, as probiotics complement normal flora, inhibit the proliferation of pathogenic bacteria, promote maturation of intestinal tract, enhance the intestinal mucosal barrier function and improve immune system function by modulating TLR4 receptor and NF- κ B and reducing intestinal bacterial translocation. Therefore, probiotics can effectively reduce the morbidity and fatality rate of NEC (17). In a case study using probiotics, there were no adverse effects reported (18). However, the specific kind of probiotics as well as the dosage and time of administration need to be determined. Recently, it has been proposed that the application of epidermal growth factor (EGF) could prevent and treat NEC by reducing inflammatory response, enhancing intestinal tract barrier function and maintaining the balance between epithelial autophagy and apoptosis (19). However, detailed studies using a larger population are required to validate these results and further understand the preventive effect of EGF.

CONCLUSION

In conclusion our study demonstrates that a multipronged approach is required for the effective treatment of NEC in both premature as well as term infants. Prevention of NEC by providing appropriate care during the perinatal period as well as early detection and treatment could greatly reduce the morbidity and mortality.

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AUTHORS' NOTE

Wanxian Zhang performed the statistical analysis, Xuehua Liu conceived of the study, Jiayi Tian participated in its design and wrote this paper ,Chaoying Yan read and approved this study.The authors declare that they have no conflicts of interest.

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