



Neonatal

Necrotizing enterocolitis as a prognostic factor for the neurodevelopmental outcome of preterm infants - match control study after 2 years



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ABSTRACT

Purpose: Necrotizing enterocolitis (NEC) in very low birth weight infants is a risk factor for developmental delay. To our knowledge, there are no studies published investigating the neurodevelopmental outcome of patients with NEC comparing surgically treated and conservatively treated patients versus match paired controls. The aim of this retrospective case control study was to measure the neurodevelopmental outcome of patients with NEC who were treated surgically or conservatively.

Methods: All patients were identified, who have been diagnosed with NEC (ICD-10 code, P77) born between 2006 and 2013. Patients with NEC received antibiotic therapy, nasogastric decompression and fasting. Surgical treatment was indicated for patients with Bell stages IIIb. We excluded patients suffering from other relevant diseases with a possible impact on their neurodevelopmental outcome (e.g., intraventricular hemorrhage, associated malformations, asphyxia, focal intestinal perforation, short bowel syndrome). Patients were tested at the corrected gestational age of 24 months according to the Bayley Scales of Infant Development II. Each participant was compared to a child of the same sex, gestational age at birth (+/− two days), birth weight (+/− 10%), and age at neurodevelopmental testing (IRB approval, No. 14/2014). The outcome measures were the psychomotor index (PDI) and the mental developmental index (MDI).

Results: We included 13 conservatively and 24 surgically treated patients. The patients in group A (without surgery) achieved a mean PDI of 106, and those in group B (with surgery) a mean PDI of 90. These values were significantly higher in the conservative group A. The mean MDIs were 99 in the patient group A and 85 in patient group B. This difference was also significant.

Conclusion: We found significantly lower MDIs and PDIs in children with surgical treatment of NEC. Further systematic prospective research on the prevention of NEC and systematic follow-ups at later stages in the patients' development are necessary in order to implement early intervention.

Type of study: case control study.

Level of evidence: III.

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Necrotizing enterocolitis (NEC) remains a devastating disease with very high morbidity and mortality. The mean incidence of the disease is approximately 5–7% among patients with birth weights between 500 g and 1500 g, and this incidence has not exhibited any improvement in recent years [1,2].

The mortality of patients suffering from NEC is considered to be 20–30% [3,4]. Conservative treatment (fasting, gastric tube placement, broad-spectrum antibiotics, parenteral nutrition, fluid resuscitation) is

the first-line therapy, but up to 50% of all patients with NEC require surgery [5]. The indication for surgery is usually based on the Bell criteria, with an absolute indication for urgent surgical intervention for Bell stage IIIb (free intraabdominal air) and a relative indication for Bell stage IIIa combined with clinical deterioration of the infant despite maximal conservative therapy [6]. There is ongoing controversy regarding the mode of surgical treatment (primary laparotomy vs. peritoneal drainage) of NEC in extremely low birth weight (ELBW) infants (< 1000 g). Primary laparotomy in infants with NEC has been reported to be associated with 35–50% mortality in different studies [7,8]. However, surgical treatment of NEC, regardless of whether peritoneal drainage or laparotomy is applied, has an overall mortality rate of 32–39% [9,10]. The outcome of affected infants is not influenced by age or weight at surgery but by the length of the necrotic bowel [11].

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It has been previously demonstrated that survivors of NEC might suffer from long-term neurodevelopmental problems. Nevertheless, there are no systematic studies on the question of possible long-term differences in neurological and somatic development of patients with conservatively or surgically treated NEC as the only complication of prematurity.

The aim of this study was to investigate the long-term neurodevelopment infants with conservatively treated NEC versus surgically treated NEC and respective age-matched controls.

1. Material and methods

The retrospective case–control analysis was approved by the Ethics Committee of the Faculty of Medicine, J.W. Goethe University Frankfurt/M. (IRB approval, No. 14/2014).

All patients were identified with various stages of NEC using the ICD-10 code P77, born during the time period of 2006 to 2013. All patients received antibiotic therapy, nasogastric decompression and fasting. These patients were also treated by circulatory support and transfusions. Surgical treatment was indicated for Bell stage IIIb. We excluded all patients with other relevant diseases or complications with a possible effect on neurodevelopment (i.e., intraventricular hemorrhage, associated malformations, asphyxia, genetic defects or serious complications, such as ROP, BPD, focal intestinal perforation, short bowel syndrome or a pathological hearing test).

The neonatal characteristics and neonatal outcomes were obtained by reviewing the patients' charts. The patient characteristics included sex, gestational age at birth, anthropometric measures at birth, maternal age, maternal gravidity and parity status, delivery mode and APGAR score, stage of disease (Bell stages), number of septic episodes and length of parenteral nutrition (PN). All selected patients had regular follow-up visits at the corrected age of approximately 24 months.

The study groups were defined as group A (conservatively treated NEC) and group B (surgically treated NEC).

Great effort was put in the selection of matched pairs to form the control group, since the group of premature infants was not conforming to the Gaussian distribution. Therefore, the control group had to be selected based on main features. Each study participant was compared against a matched child of same sex, same gestational age at birth ($\pm$ two days), same birth weight ($\pm$ 10%), same age at neurodevelopmental testing (same analysis group of BSID-II), but without NEC. Many patients were multiples, the respective siblings were taken as an optimally matched pair, as their genetic pool was identical. The control group was divided in sub-group a (to be compared with the group A of conservatively treated NEC patients) and sub-group b (comparison to group B).

1.1. Neurodevelopmental assessment

All study participants underwent neurodevelopmental testing with the Bayley Scales of Infant Development II Assessment (BSID-II) to measure cognitive and psychomotor development. A specialized child psychologist performed the BSID-II. The BSID-II assessment provided a mental developmental index (MDI), which was detected by testing verbal and nonverbal abilities. Furthermore, the BSID-II provided a psychomotor developmental index (PDI), which was established by test items concerning gross and fine motor function. Both the MDI and PDI had means (SDs) in the normative population of 100 (15). An index score of -1 to -2 SD was classified as mildly delayed performance, whereas an index score of -2 SD or less was classified as severely delayed performance. Verbal and non-verbal abilities as well as gross and fine motor function were expressed as percentages. Furthermore, a detailed medical history concerning the time after discharge was taken, a medical examination was performed and anthropometric data were obtained by a pediatrician who also evaluated whether the BSID-II results seemed to be consistent with the child's clinical impression.

1.2. Data analysis

For the statistical analysis of the differences between the patient group and the healthy peers, we used the Mann–Whitney U test. To analyze the correlations between the need for parenteral nutrition and the neurodevelopmental indices in our patient group, the Spearman rank correlation coefficient was used. P-values <0.05 were considered statistically significant. The statistical analyses were performed using BiAS v10.02 software.

2. Results

We treated 278 infants below 1500 g in our institution between 2006 and 2013. From those 69 patients were diagnosed with NEC in this time period. 49/69 patients with NEC were referred from other institutions. We excluded 32 patients with other relevant diseases or complications with a possible effect on neurodevelopment. We included altogether 37 patients with NEC in the study. 13 patients were assigned to group A (conservatively treated NEC), from whom 10 patients presented with Bell stage 2, and 3 patients with Bell stage 3a. 24 NEC patients were included in group B (surgical treatment) and 37 matched pairs were included in the control groups (a/b).

Neonatal data and outcome are given in Table 1. All relevant baseline characteristics of the patients and the match pair controls group were not statistically significant (Table 1). None of the study participants suffered from hearing impairment.

2.1. Neurodevelopmental Outcome

The neurodevelopmental outcome was determined by the BSID-II.

The outcome was split into the psychomotor index (PDI) and mental developmental index (MDI). Comparing all NEC patients with healthy infants, significant difference was found in the mean MDI ($p = 0.008$) 90 (95% CI 50–122) in the combined patient group A + B and 100 (95% CI 52–124) for the control group a + b (Table 1).

Further significant difference was observed for the solved nonverbal items ($p = 0.04$) 47% versus 66%, solved verbal items ($p = 0.067$) 45% versus 56% and the time up to total nutrition ($p < 0.001$) for the combined patient group A + B and control group a + b (Table 1).

When looking at patient group A and control group a the only statistically significant difference could be found in the time to total enteral nutrition ($p = 0.011$) with a mean of 42 days (23–72) versus 21 days (5–46), showing that conservatively treated NEC patients had an allover acceptable outcome (Table 2).

The results of the comparison of patient group B with control group b a significant reduction of mean MDI ($p = 0.02$) of 85 (95% CI 50–118) versus 101 (95% CI 70–124), solved nonverbal items ($p = 0.009$) 51% versus 66%, solved verbal items ($p = 0.038$) 40% versus 56%. Highly significant was the time to total enteral nutrition ($p < 0.001$) with a mean 50 days (12–120) versus 20 days (1–40) (Table 3).

Comparing the two patient groups A and B, significant differences could be found in the mean PDI ($p = 0.032$) 106 (95% CI 84–128) versus 90 (95% CI 50–132), the mean MDI ($p = 0.020$) 99 (95% CI 74–122) versus 85 (95% CI 50–118) and solved nonverbal items ($p = 0.031$) 69% versus 51% (Table 4).

The number of patients and controls who showed a normal development compared to those with mild or severe delay is displayed in Table 5. These results show, that the majority of all patients, including the patients with surgical NEC achieved a normal development or mild delayed development. (Table 5).

3. Discussion

This study is a retrospective case–control analysis of the long-term outcomes of children with NEC (conservatively or surgical treated) as a complication during the neonatal period. We could show that NEC

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