Journal of Pediatric Surgery 53 (2018) 1197–1202

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Growth morbidity in extremely low birth weight survivors of necrotizing enterocolitis at discharge and two-year follow-up☆

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ARTICLE INFO

Article history:
Received 19 February 2018
Accepted 27 February 2018

Key words:
Necrotizing enterocolitis
Extremely low birthweight
Surgery
Growth failure
Neonatal intensive care unit
Follow-up

ABSTRACT

Purpose: The purpose of this study was to examine postnatal growth outcomes and predictors of growth failure at 18–24 months corrected age among extremely low birth weight (ELBW) survivors of necrotizing enterocolitis (NEC) compared to survivors without NEC.
Methods: Data were collected prospectively on ELBW (22–27 weeks gestation or 401–1000 g birth weight) infants born 2000–2013 at 46 centers participating in the Vermont Oxford Network follow-up project. Severe growth failure was defined as <3rd percentile weight-for-age.
Results: There were 9171 evaluated infants without NEC, 416 with medical NEC, and 462 with surgical NEC. Rates of severe growth failure at discharge were higher among infants with medical NEC (56%) and surgical NEC (61%), compared to those without NEC (36%). At 18–24 months follow-up, rates of severe growth failure decreased and were similar between without NEC (24%), medical NEC (24%), and surgical NEC (28%). On multivariable analysis, small for gestational age, chronic lung disease, severe intraventricular hemorrhage or cystic periventricular leukomalacia, severe growth failure at discharge, and postdischarge tube feeding predicted <3rd percentile weight-for-age at follow-up.
Conclusions: ELBW survivors of NEC have higher rates of severe growth failure at discharge. While NEC is not associated with severe growth failure at follow-up, one quarter of ELBW infants have severe growth failure at 18–24 months.
Type of study: Prognosis study.
Level of evidence: II

Extremely low birth weight (ELBW) infants are at significant risk for postnatal growth failure, particularly infants with necrotizing enterocolitis (NEC), an inflammatory/infectious condition affecting the newborn gut [1]. NEC preferentially affects premature and low birth weight infants, with an incidence up to 12% and mortality in the 30%–40% range for 501–1000 g birth weight infants [2]. NEC leads to impaired enteral nutritional intake through numerous mechanisms, such as associated prolonged periods of bowel rest, bowel resection, short bowel syndrome, malabsorption, postoperative bowel obstruction, and strictures. NEC during the neonatal hospital course is associated with poorer postnatal growth, with an even greater reduction in discharge weight Z-scores for surgical NEC [1,3]. We sought to examine growth at two-year follow-up in surviving ELBW infants with a history of NEC, compared to those without a history of NEC.

1. Methods

1.1. Patient population

This analysis used prospectively collected data on ELBW infants (birthweight 401–1000 g or 22–27 weeks gestational age at birth) born between 2000 and 2013 at 46 North American centers participating in the Vermont Oxford Network (VON) ELBW infant follow-up project. Infants who survived and underwent follow-up evaluation at 18–24 months corrected age were included. Infants with a major congenital anomaly, initial hospital length of stay <72 h, or missing information on NEC surgery or final disposition were excluded. Surviving ELBW infants without a history of NEC served as the control population.

☆ Disclosures: K. A. Morrow, K. R. Ferrelli, R. F. Soll, and J. D. Horbar are employees of Vermont Oxford Network. E. M. Edwards is supported by a grant from the Vermont Oxford Network to the University of Vermont. B. S. Fullerton is supported by the Boston Children's Hospital Department of Surgery Chair's Research Fellowship

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https://doi.org/10.1016/j.jpedsurg.2018.02.085
0022-3468/

1.2. Data collection and definitions

VON is a nonprofit voluntary clinical collaborative of centers dedicated to quality improvement in neonatal intensive care. VON member hospitals submit deidentified data that are prospectively collected by local staff using uniform definitions until neonates are discharged from the hospital, die, or reach one year of age in the hospital. Records are automatically checked and returned for correction if incomplete.

Of 753 North American VON centers, 46 participate in the ELBW infant follow-up project (Appendix, online only). These centers conduct detailed follow-up evaluations of ELBW infants at 18–24 months corrected age, which include assessment of home living situation, caregiver sociodemographics, healthcare needs such as rehospitalizations or postdischarge surgeries, developmental status, and weight. Follow-up is coordinated by participating centers and informed consent for inclusion in the ELBW infant follow-up project is obtained according to each center's Institutional Review Board (IRB). All ELBW infants discharged from the hospital alive are followed and the status at time of follow-up is reported as dead, alive, or unknown.

Standardized data collection forms were used across all VON centers [4]. Small for gestational age (SGA) was defined as weight < 10th percentile for gestational age. A clinical diagnosis of NEC required at least one physical finding (bilious gastric aspirate or emesis, abdominal distention, or occult/gross blood in stool with no anal fissure) and one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum), that is at a minimum Bell's Stage II [5]. The VON definition of surgery for NEC, suspected NEC, or bowel perforation in the VON database required at least one of the following: laparotomy, bowel resection, or intraperitoneal drain placement. Spontaneous intestinal perforation (SIP) was diagnosed based on visual inspection of the bowel at the time of laparotomy or postmortem examination. For our analyses, surgical NEC included infants with NEC or SIP who required laparotomy, bowel resection, or intraperitoneal drain placement. Consistent with prior VON studies, SIP was included in the surgical NEC group as SIP and NEC cannot be differentiated among infants who undergo only peritoneal drain placement.

Follow-up data items are defined in the ELBW Infant Follow-up Manual of Operations [4]. Maternal age at birth, and household income in relation to federal poverty guidelines (for US centers), were not collected until 2006 and onward. Rehospitalization and postdischarge surgery data items include write-in fields, which were reviewed by investigators at Boston Children's Hospital and categorized appropriately.

This study was part of an ongoing collaboration between VON and Boston Children's Hospital. The Committee on Human Research at the University of Vermont approved the use of the VON Research Repository for this analysis (#15-143). This study was exempt from Boston Children's Hospital IRB review (#P00002185) based on use of existing deidentified data.

1.3. Study outcomes

Weight data from discharge and 18–24 months corrected age were examined. Weight-for-age percentiles were calculated using Fenton preterm standards up to 50 weeks postmenstrual age and CDC standards after 50 weeks postmenstrual age, corrected for prematurity. Severe growth failure was defined as <3rd percentile weight-for-age.

1.4. Statistical analysis

Data are presented as N and percentage or median (Q1, Q3) where applicable. Statistical differences in characteristics and outcomes between infants with no NEC, medical NEC, and surgical NEC were evaluated using chi-squared tests or Kruskal–Wallis tests. In Table 2, we tested for differences in the major categories only (any outpatient support, any medical rehospitalization, and any surgery after discharge) owing to concerns about multiple comparisons. Adjusted risk ratios with 95% confidence intervals (ARR, 95% CI) were calculated using generalized estimating equations controlling for clustering of infants within hospitals to ascertain predictors of severe growth failure at follow-up. Models included NEC status, sex, small for gestational age, any sepsis, chronic lung disease, severe intraventricular hemorrhage or cystic periventricular leukomalacia, severe retinopathy of prematurity, any human milk at initial discharge, severe growth failure at initial discharge, maternal age, parental education, poverty level, feeding support at follow-up, rehospitalizations after initial discharge, and surgery after initial discharge. Data analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

2. Results

2.1. Infant characteristics and hospital course

There were 3137 ELBW infants with NEC seen at centers participating in the infant follow-up project, of which 202 were excluded for other congenital anomalies, length of stay less than 72 h, or missing data on NEC surgery or final disposition. Of the 2935 eligible infants, 1380 survived to follow-up, with a survival rate of 49% for infants with a history of medical NEC and 45% for infants with a history of surgical NEC. Among the eligible infants that survived to follow-up, 416 (69%) with medical NEC and 462 (60%) with surgical NEC were evaluated at 18 to 24 months corrected age (Fig. 1). There were 21,329 eligible ELBW infants at infant follow-up centers who did not have NEC, of which 13,223 (62%) survived to follow-up, and 9171 (69%) of the survivors were evaluated at 18 to 24 months corrected age. Infant characteristics and clinical course until initial hospital discharge for each evaluated group are detailed in Table 1. Infants with a history of surgical NEC had the highest rates of sepsis, chronic lung disease, severe intraventricular hemorrhage (IVH) or cystic periventricular leukomalacia (PVL), and severe retinopathy of prematurity. The longest lengths of stay and lowest rates of receiving breast milk were also seen among infants who had surgical NEC. Within the surgical NEC cohort, 30% underwent primary peritoneal drainage. While the proportion of infants undergoing only primary peritoneal drainage who had SIP is not known, laparotomy confirmed SIP comprised 31% of the surgical NEC cohort.

2.2. Socioeconomic characteristics and postdischarge healthcare needs

Socioeconomic characteristics assessed are listed in Table 2. Primary caregiver education was less than high school for 9% of ELBW infants without NEC (N = 8539), 11% for medical NEC (N = 372), and 11% for surgical NEC (N = 419). Families with income below US Department of Health and Human Services (HHS) poverty level comprised 33% of the no NEC group (N = 4400), 37% of the medical NEC group (N = 170), and 37% of the surgical NEC group (N = 296). While we observed high rates of outpatient medical support, rehospitalization, and surgery after discharge among all ELBW infants, those who had a history of surgical NEC had the greatest healthcare needs. Among ELBW infants with a history of surgical NEC, 25% had gastrostomy or nasogastric feeding, 8% were rehospitalized for nutritional problems or failure to thrive, and 48% had surgery after discharge (Table 2).

2.3. Growth outcomes of ELBW infants evaluated at follow-up

Among eligible ELBW infants followed who had discharge weight data from their initial hospitalizations, 36% of infants with no NEC (N = 7300), 56% of infants with medical NEC (N = 326), and 61% of infants with surgical NEC (N = 341) had severe growth failure at initial discharge (chi-square = 135.6, df = 2, $p < 0.0001$). Follow-up evaluation occurred at a median of 20 months (19, 22) corrected age for all three groups and 98% had weight data collected at follow-up. Rates of severe growth failure at follow-up were similar between the three groups: 24% for no NEC, 24% for medical NEC, and 28% for surgical