Brain Magnetic Resonance Imaging in Infants with Surgical Necrotizing Enterocolitis or Spontaneous Intestinal Perforation versus Medical Necrotizing Enterocolitis

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Magnetic resonance imaging of the brain was performed in 26 preterm infants with necrotizing enterocolitis (NEC) or spontaneous intestinal perforation at term equivalent age. Infants with surgical NEC or spontaneous intestinal perforation had significantly more brain injury on magnetic resonance imaging compared with infants with medical NEC, even after adjustment for confounders. *(J Pediatr 2014;164:410-2).*

Preterm infants with necrotizing enterocolitis (NEC) are known to have worse neurodevelopmental outcomes than gestational age (GA)-matched controls,[1,2] and infants with surgical NEC have worse outcomes than those with medical NEC.[1-3] Adverse neurodevelopmental outcomes of infants with NEC appear to be mediated by white matter injury.[4] We hypothesized that compared with infants with medical NEC, infants with surgical NEC or spontaneous intestinal perforation (SIP) would have more severe brain injury detected on magnetic resonance imaging (MRI) at term.

Methods

A clinical protocol was instituted in our neonatal intensive care unit (NICU) to perform brain MRI at term on all surviving infants with NEC/SIP. MRI analysis and chart review were approved by the local Institutional Review Board. Clinical variables included GA at birth, birth weight, antenatal steroids, small for gestational age (SGA) status, singleton status, days of mechanical ventilation (MV), positive blood culture, meningitis, bronchopulmonary dysplasia (BPD), days of total parenteral nutrition, weight z-score at 40 weeks, postnatal steroids for BPD, surgery for patent ductus arteriosus, and need for pressors. Infants with confirmed NEC (Bell stage II[5] or higher) or SIP were included. MRI sequences included sagittal T1 spin echo, axial T1 fluid-attenuated inversion recovery, axial T2/proton density fast-spin echo (FSE), coronal T2 FSE, sagittal T2 FSE, axial susceptibility-weighted angiography, and 15-direction diffusion tensor imaging. The degree of brain injury was assessed by 2 blinded neuroradiologists using a white matter injury scoring system modified from Miller et al[6] with the addition of intraventricular hemorrhage and cerebellar hemorrhage (**Figure 1**).

The Fisher exact or Wilcoxon rank-sum test was used to identify differences in clinical variables between the medical NEC group and the surgical NEC/SIP group. Spearman ρ and point biserial correlation coefficients were calculated to determine variables related to brain injury score. A general linear regression model was developed to predict the outcome of brain injury score using the type of NEC/SIP as the main effect and potential confounder variables as covariates. Because the injury score was not normally distributed, a square root transformation was performed, and the transformed variable was used in the linear regression. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Of 29 infants with NEC/SIP who survived to term, 26 (15 with medical NEC, 6 with surgical NEC, and 5 with SIP) underwent brain MRI and were included in the study. Perinatal characteristics of the infants with medical NEC and those with surgical NEC/SIP are shown in the **Table** (available at www.jpeds.com). Demographic data and NICU courses were similar in the 2 groups, although the infants with surgical NEC/SIP had more days of MV and were more likely to require pressor therapy.

Brain injury scores in the total cohort ranged from 0 to 11. Birth weight (Spearman $\rho = -0.41$; $P = .036$), GA (Spearman $\rho = -0.39$; $P = .046$), days of MV (Spearman $\rho = 0.41$; $P = .035$), and BPD (point biserial $\rho = 0.39$; $P = .046$) were correlated with total injury score. The unadjusted mean brain injury score was significantly higher for infants with surgical

BPD	Bronchopulmonary dysplasia
FSE	Fast-spin echo
GA	Gestational age
MRI	Magnetic resonance imaging
MV	Mechanical ventilation
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
SGA	Small for gestational age
SIP	Spontaneous intestinal perforation

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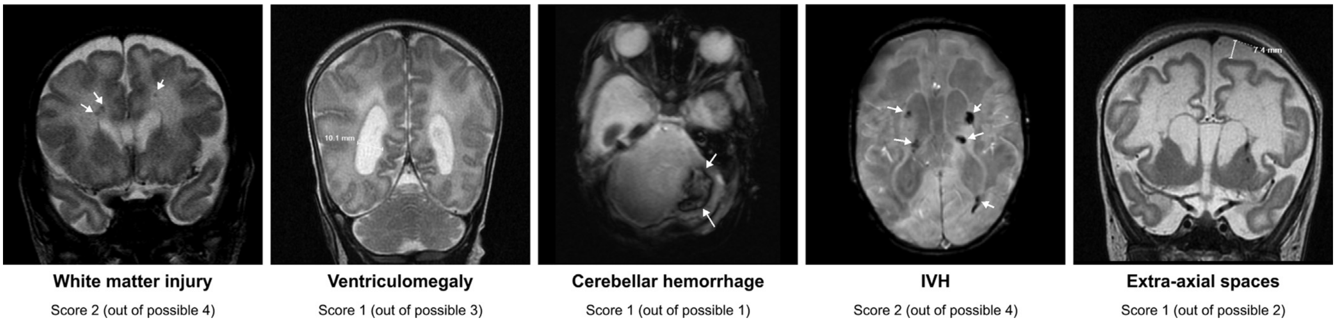

Figure 1. Example brain injury scores. *IVH*, intraventricular hemorrhage.

NEC/SIP compared with infants with medical NEC (P = .001). After controlling for SGA, days of MV, and weight z-score at 40 weeks, the difference in brain injury score between the 2 groups remained significant (P = .032) (**Figure 2**). Other potential confounders were not significant in the multiple regression model.

Although we elected to combine the surgical NEC and SIP groups, we also examined the differences among infants with medical NEC, infants with surgical NEC, and infants with SIP using a scatterplot of brain injury scores (**Figure 3**; available at www.jpeds.com).

Discussion

In this study, compared with infants with medical NEC, infants with surgical NEC or SIP had more severe brain injury detected on MRI at term, even after controlling for potential confounding factors. Our findings suggest a mechanistic explanation for the observations that infants with surgical NEC[1-3] and SIP[7,8] have poorer outcomes than infants with medical NEC, who in turn have poorer outcomes than GA-matched controls.[1,2]

Infants with NEC of sufficient severity to require surgery are likely sicker than those with medical NEC. We attempted to control for this by including positive blood cultures and the need for pressors, but neither of these potential confounders was significant in the final model. Infants with more severe NEC or SIP are likely to have increased circulating inflammatory mediators. Plasma levels of cytokines correlate with disease severity in infants with NEC.[9,10] Systemic inflammation is known to contribute to neuronal injury,[11,12] possibly owing to proinflammatory cytokines from microglial cells injuring preoligodendrocytes,[13] leading to white matter injury.

Nutritional factors are another possible explanation for the worse brain injuries in the surgical NEC group. Both SGA and weight-for-age z-score at 40 weeks were significant in the final model. Infants with poorer growth in the NICU have worse neurodevelopmental outcomes,[14] and preterm infants with better nutrition in the first 28 days of life have greater total brain volume on MRI at term equivalent age.[15]

Finally, it is possible that the surgery itself could have contributed to the worse brain injuries in infants with surgical NEC and SIP. Anesthetics can be toxic to the developing brain,[16] and an association between anesthetic exposure and smaller gray matter volumes on brain MRI in preterm infants has been suggested.[17] However, 40% of the infants with medical NEC eventually underwent surgery for stricture resection, and thus if it were the anesthesia or surgery that contributed to the brain injury, we would expect to see worse brain injury scores in these infants as well.

Limitations of the present study include its small sample size and lack of control group, owing to the selected population in our level IV NICU. Strengths of the study include capturing almost all surviving infants with NEC or SIP, extensive chart review, and consistency of age at MRI.

In conclusion, compared with preterm infants with medical NEC, those with surgical NEC/SIP have more severe brain injury detected on brain MRI at term. This study provides further information on the anatomic correlates[18] of poor neurodevelopmental outcomes in infants with surgical

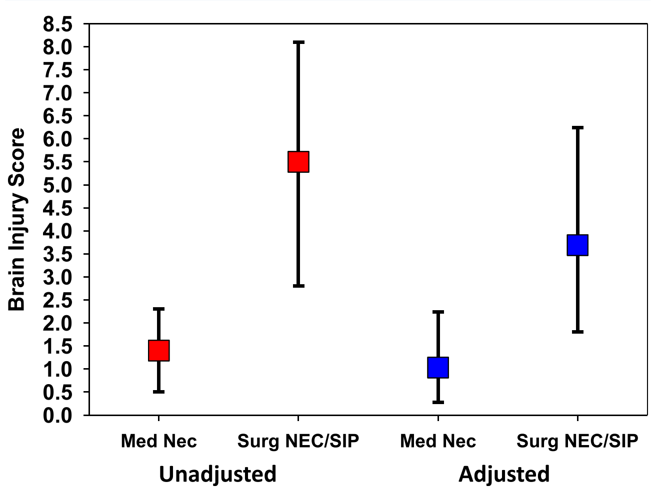

Figure 2. Brain injury scores in infants with medical NEC vs those with surgical NEC/SIP, unadjusted analysis and after adjustment for possible confounding variables.