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Surgery and Neurodevelopmental Outcome of Very Low Birth Weight Infants

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Abstract

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IMPORTANCE—Reduced death and neurodevelopmental impairment among infants is a goal of

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perinatal medicine.

OBJECTIVE—To assess the association between surgery during the initial hospitalization and death or neurodevelopmental impairment of very low birth weight infants.

DESIGN—Retrospective cohort analysis of patients enrolled in the National Institute of Child Health and Human Development Neonatal Research Network Generic Database from 1998–2009 and evaluated at 18–22 months' corrected age.

SETTING—22 academic neonatal intensive care units.

PARTICIPANTS—Inclusion criteria were: birth weight 401–1500 g; survival to 12 hours; available for follow-up. Some conditions were excluded. 12 111 infants were included in analyses, 87% of those eligible.

EXPOSURES—Surgical procedures; surgery also classified by expected anesthesia type as major (general anesthesia) or minor surgery (non-general anesthesia).

MAIN OUTCOME MEASURES—Multivariable logistic regression analyses planned *a priori* were performed for the primary outcome of death or neurodevelopmental impairment and for the secondary outcome of neurodevelopmental impairment among survivors. Multivariable linear regression analyses were performed as planned for the adjusted means of Bayley Scales of Infant Development, Second Edition, Mental Developmental Index and Psychomotor Developmental Index for patients born before 2006.

RESULTS—There were 2186 major, 784 minor and 9141 no surgery patients. The risk-adjusted odds ratio of death or neurodevelopmental impairment for all surgery patients compared with those who had no surgery was 1.29 (95% confidence interval 1.08–1.55). For patients who had major surgery compared with those who had no surgery the risk-adjusted odds ratio of death or neurodevelopmental impairment was 1.52 (95% confidence interval 1.24–1.87). Patients classified as having minor surgery had no increased adjusted risk. Among survivors who had major surgery compared with those who had no surgery the adjusted odds ratio for neurodevelopmental impairment was 1.56 (95% confidence interval 1.26–1.93) and the adjusted mean Mental Developmental Index and mean Psychomotor Developmental Index values were lower.

CONCLUSIONS AND RELEVANCE—Major surgery in very low birth weight infants is independently associated with a greater than 50% increased risk of death or neurodevelopmental impairment and of neurodevelopmental impairment at 18–22 months' corrected age. The role of general anesthesia is implicated but remains unproven.

Administration of general anesthetic agents to developing animals induces increased neuroapoptosis and subsequent neurocognitive or behavioral deficits.[1–10] The toxic effects are widespread and affect both neurons and oligodendrocytes.[11, 12] The doses used to produce neurotoxic effects are analogous to those used in the clinical setting. The peak vulnerability to neuroapoptotic injury in rodents occurs at a stage of brain development equivalent to early gestation through infancy in humans.[7] In contrast to general anesthesia, spinal anesthesia in developing rats does not produce increased neuroapoptosis and is not associated with recognized subsequent abnormality.[13]

These experimental observations raise concern that exposure of infants to general anesthesia for surgical procedures may increase the risk of subsequent neurodevelopmental impairment (NDI).[14–16] A study of infants who were born in 1985–1988 weighing <1000 g or who were <27 weeks' gestational age found an adverse association of surgery requiring general anesthesia and moderate or severe disability at age 5 years, with adjusted odds ratio (AOR) = 10.1; 95% confidence interval (CI) = 2.3–44.[17] However, a smaller study of infants born between 2001–2004 weighing <1250 g or <30 weeks' gestational age found no significant effect on neurodevelopmental outcomes at age 2 years, although the infants exposed to surgery had relatively smaller brain volumes and more white matter injury.[18] Several of the indications for surgical procedures in neonates, such as congenital malformations and necrotizing enterocolitis, have increased risk-adjusted odds of neonatal death as great as three-fold.[19] Postoperative neonates have a 40% increased adjusted risk of life-threatening infection.[20] To determine in a large cohort of very low birth weight (VLBW) infants exposed to surgical procedures if there were an increased adjusted risk for death or NDI at 18–22 months' corrected age (CA), we conducted a retrospective analysis of the patients enrolled in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) Generic Database (GDB).

Methods

Subjects

We studied VLBW infants enrolled in the NRN GDB from 1998 through 2009 who had birth weights (BW) of 401–1500 g, survived 12 hours and were available for follow-up assessments at 18–22 months' CA. We excluded patients who had certain conditions (eTable 1); among the excluded patients were those with congenital heart defects (CHD) and those who had surgery for a patent ductus arteriosus (PDA), conditions associated with NDI.[21–24] The follow-up evaluation included neurologic, hearing, vision and developmental assessment.[25] Centers received local institutional review board approval for data collection.

Sample size

During 1998–2009, there were 12 111 infants of BW 401–1500 g with complete data who were included in the analyses, and 2970 of these had surgery during the initial hospitalization (eFigure).

Definitions

The primary outcome was death before follow-up assessment or NDI at 18–22 months' CA. Because the NRN instrument used in neurodevelopmental assessment changed during the study period, NDI for infants born from 1998–2005 was defined as one or more of: Bayley Scales of Infant Development, Second Edition (BSID II) Mental Developmental Index (MDI) score <70 or Psychomotor Developmental Index (PDI) score <70; Gross Motor Function Classification System (GMFCS) ≥ level 2; moderate or severe cerebral palsy; bilateral blindness; or hearing impairment with hearing aids in both ears. For infants born from 2006–2009, NDI was defined as one or more of: Bayley Scales of Infant and Toddler Development, Third Edition (BSID III) cognitive composite score <80; GMFCS ≥ level 2; moderate or severe cerebral palsy; deafness (permanent hearing loss that does not permit the

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child to understand the directions of the examiner and communicate despite amplification); or blindness (some or no useful vision in either eye). Secondary outcomes were: NDI and its components among survivors; and for infants born before 2006, mean MDI and PDI scores.

The principal risk factor was surgery. For some analyses, surgery was classified into two subgroups, major and minor surgery. The GDB includes data for specific surgical procedures but not for anesthesia. Minor surgery was defined as a procedure that could have been performed under neuraxial, regional, or local anesthesia, such as gastrostomy, peritoneal drain placement, and inguinal hernia repair. Major surgery was defined as surgery that usually is performed with general anesthesia. Major surgery procedures also are more substantial than minor surgery procedures in aspects other than anesthetic agent, such as duration, physiologic stress and postoperative analgesia. The GDB includes annotations regarding some circumstances under which surgery was performed, including general anesthesia used for procedures that are usually performed with non-general anesthesia.

Severe intracranial hemorrhage (ICH) was defined as parenchymal or intraventricular hemorrhage with ventricular dilatation, or cystic periventricular leukomalacia (cPVL). Bronchopulmonary dysplasia (BPD) was defined as requiring supplemental oxygen at 36 weeks. Necrotizing enterocolitis (NEC) was defined as modified Bell classification stage II A or higher.[26]

Analysis

Chi-square and Fisher's exact tests were used for categorical variables; analysis of variance tests were used for continuous variables. Separate bivariate analyses were performed to assess associations between the primary and secondary outcomes, respectively, and the main predictors, as well as with potential confounders related to surgery and baseline covariates. To adjust for possible selection bias for performance of surgery, we developed a propensity score (PS) modeling approach.[27–30] We first attempted to develop a 3-level prediction model for the risk of surgery using proportional odds logistic regression. The proportionality assumption was not satisfied by the data, so we considered a polytomous logistic regression using a generalized logit model.

Once a prediction model for 3-level risk of surgery was developed by obtaining the PS for major, minor and no surgery, we performed a multivariable logistic regression analysis of death or NDI, including adjustment with the PS of major and minor surgeries, as well as baseline covariates. We adjusted for NRN center and also for birth-year cohort effect to account for differences between the BSID II and the BSID III instruments.[25, 31] We performed a similar multivariable logistic regression analysis for the outcome of NDI among survivors. In additional analyses of survivors who were evaluated with the BSID II scales at 18–22 months' CA, multivariable linear regression analyses were performed to determine separately for adjusted mean MDI and adjusted mean PDI the significance and contribution of surgery. These analyses included the PS of major and minor surgery and all of the other variables associated with NDI from the bivariate analyses. SAS Version 9.2 (Cary, NC) was used for statistical analyses.

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Results

Patient characteristics

The analyses included 2186 patients with major surgery, 784 with minor surgery and 9141 patients with no surgery. The patients in these three categories differed in most characteristics (Table 1). The 4649 procedures that we classified as major or minor surgery (eTable 2) were unequally distributed among anatomical systems (eTable 3). Most subjects who had surgery had only a single exposure, but 1080 subjects had multiple exposures (eTable 3).

Unadjusted outcomes

Unadjusted associations of the 3-level surgery exposure and, respectively, death or NDI; NDI among survivors; mean scores for BSID II MDI and PDI and BSID III cognitive composite score; GMFCS level ≥2; moderate or severe cerebral palsy; blindness; and deafness (Table 2) exhibit a progressively greater incidence of the respective adverse outcome from the no surgery, to the minor surgery, and to the major surgery subgroups.

Multivariable logistic regression analyses

In a multivariable logistic regression analysis of the primary outcome in which all surgery patients were considered together as a risk factor (Table 3, Model 1), patients who had surgery had significantly higher adjusted odds of death or NDI compared with those who had no surgery (AOR = 1.29 (95% CI 1.08–1.55). The multivariable logistic regression analysis for the outcome NDI among survivors also indicated increased risk for NDI among all survivors who had surgery (eTable 4, Model 2).

In a multivariable logistic regression analysis of the outcome death or NDI when surgery procedures are classified as major or minor (Table 4, Model 3), patients who had major surgery had significantly higher adjusted odds of death or NDI compared with those who had no surgery (AOR = 1.52 (95% CI 1.24–1.87) and also compared with those who had minor surgery (AOR = 1.45 (95% CI 1.14–1.85). There was no significant difference in death or NDI for patients who had minor surgery compared with those who had no surgery. There were increasing adjusted odds of death or NDI with increasing number of separate surgeries. In a multivariable logistic regression analysis for the outcome NDI among survivors there was an increased adjusted risk of NDI among survivors who had major surgery compared with those who either had no surgery or minor surgery (eTable 5, Model 4). eTable 6 presents evidence that the PS achieved balanced distribution of covariates among the surgery groups.

We performed a sensitivity analysis in which patients who had surgery for retinopathy of prematurity (ROP) and were initially classified as major surgery patients were excluded, reasoning that there might be a strong possibility for confounding by indication. That is, patients who had ROP sufficiently severe to warrant surgery had a high probability before surgery of having impaired vision and thus NDI. The exclusion of ROP surgery patients did not qualitatively change the primary outcome death or NDI calculated using Model 3. A second sensitivity analysis was performed in which we excluded 123 severe ICH patients

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who had shunt procedures, and the primary outcome result was qualitatively unchanged. A third sensitivity analysis was performed in which the classification of 392 patients who had procedures to repair inguinal hernia, gastroschisis or omphalocele was changed from minor to major surgery. With this change there was no significantly increased adjusted risk of death or NDI for major surgery patients compared with no surgery patients, using Models 3 and 4, suggesting a relatively low adverse risk for this group of procedures and also that the association between general anesthesia and the primary outcome is dependent on the specific surgical procedure, i.e., effect modification. One possible explanation for the effect modification is the length of the procedure and exposure to anesthesia associated with various procedures.

Bayley II MDI and PDI

Among those to whom the BSID II was administered, the overall unadjusted mean MDI was 80.0, and the overall unadjusted mean PDI was 84.3. In multivariable linear regression analyses of mean BSID II MDI and mean PDI between groups (Table 5, Models 5 and 6), major surgery patients had an adjusted mean value for MDI of 3.3 (95% CI 1.4–5.1) less than that for patients who had no surgery and 3.6 (95% CI 1.5–5.6) less than that for those who had minor surgery. The adjusted mean value for PDI for major surgery patients was 3.6 (95% CI 1.8–5.4) less than that for patients who had no surgery and 3.1 (95% CI 1.0–5.2) less than that for those who had minor surgery.

Discussion

VLBW infants who underwent surgical procedures during their postnatal hospitalizations had increased adjusted risk of death or NDI at 18–22 months' CA, and survivors had increased adjusted risk of NDI. Classification to major or minor surgery groups based on expected type of anesthesia also resulted in increased adjusted risk of death or NDI for those classified as major, but not for those classified as minor surgery patients. The adjusted risk of NDI among survivors was increased for major surgery patients. Infants whose surgery could have been conducted with neuraxial, regional, or local anesthesia, classified as minor surgery, did not have significantly increased adjusted risk of either the primary or secondary outcome. Sensitivity analyses did not alter these outcomes, except when procedures to repair inguinal hernia, gastroschisis or omphalocele were reclassified from minor to major surgery, an observation of effect modification that suggests a relatively low adverse risk for this group of procedures that may be a consequence of length of exposure to anesthetic agents. Alternatively, there may be other contributors to the adverse effects of surgical procedures on the primary outcome, such as stress, unidentified physiologic alterations or effects of pharmacologic agents other than anesthetics administered to surgery patients. The adjusted means for the BSID II MDI and PDI scores at age 18–22 months were less for patients who had major surgery than for those who had minor or no surgery.

These results were observed despite adjustment for many covariates that may reflect the level of illness. The covariates in the adjustments of the regression analyses included a PS for the likelihood of having a major or minor surgical procedure, as well as variables previously demonstrated to have independent effects on the outcomes in similar study populations. The PS method provides an alternative approach to covariate adjustment that reduces the entire collection of unbalanced baseline covariates to a single score that can be used for adjustment.

Although we excluded patients who had surgery for PDA because the procedure in VLBW infants has been associated with subsequent NDI or neurosensory impairment, [23, 24] we retained patients who had PDA but no surgical closure and observed no independent increased risk of death or NDI or of NDI among survivors.

The NRN has previously reported analyses of neurodevelopmental outcomes of VLBW infants following other selected surgical procedures. In a retrospective study of NRN patients, surgery for NEC was a significant independent risk factor for MDI scores <70, PDI scores <70 and NDI compared with infants who had medically treated NEC and infants without NEC.[32] However, surgical NEC patients also had poorer growth than others. Because surgical NEC was presumably associated with greater severity of the disease, an independent effect of surgery could not be demonstrated. In a separate prospective cohort pilot study, neonates with NEC or intestinal perforation who were treated by laparotomy under general anesthesia were compared with those treated by peritoneal drain placement without general anesthesia.[33] The AOR for NDI or death by treatment group was not significant. In another NRN retrospective cohort analysis, children with severe ICH and ventriculoperitoneal shunts had significantly lower BSID II MDI and PDI scores compared with those with severe ICH and no shunt.[34]

Other retrospective analyses have examined cohorts of more mature neonates or older children who were exposed to general anesthesia from as early as during the birthing process to as old as age 5 years.[35–46] The observed outcome measures ranged from individual neurodevelopmental testing at 18–22 months to learning disabilities identified during childhood and school achievement assessed by group testing at 19 years. Most,[35–43] but not all,[44–46] studies reported worse neurodevelopmental or achievement outcomes for patients who had surgery than for others, and some reported increasing risk with multiple surgical exposures. [35, 38, 40]

It is difficult to determine if an adverse effect associated with surgery results from the anesthetic drug or from noxious effects of other perioperative drugs and/or events unrelated to the anesthetic. However, a meta-analysis of 7 selected observational studies of the effect of anesthesia with or without surgery in children ages 0–4 years on developmental or behavioral outcomes found that the summary odds ratio for adverse outcome was 1.4 (95% CI 0.9–2.2) when adjusted outcomes were considered.[47] Included among the studies selected for the meta-analysis was one that reported no increase in adjusted neurodevelopmental risk for preterm infants who received prolonged sedation and/or opioids for mechanical ventilation and/or surgery.[48] Another included study examined sedation and analgesia drugs following surgery for CHD and found no association between dose and duration of sedation/analgesia drugs and adverse neurodevelopmental outcomes.[49]

Both major surgery and ICH, which includes cPVL, are significant independent predictors of death or NDI and NDI among survivors (Table 4 and eTable 5). There are likely multiple

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pathways to NDI in preterm infants, as suggested previously by the detection of cPVL by ultrasound in only a minority of infants with abnormal neurodevelopmental outcomes.[50]

For the present analysis, the type of anesthesia was not documented, and the anesthetic agents and doses used and perioperative analgesics, sedatives and other drugs administered were not available. Of special concern is caffeine, a drug used frequently in VLBW infants, which has been shown to potentiate the neurotoxic effects of anesthetic agents in developing mice;[51] potentiation in infants has not been studied. Perioperative events such as hypoxemia, hyperoxemia, hypotension and hypothermia were not collected and could not be considered for adjustment. Notwithstanding these and other, unrecognized potential confounders, this analysis supports the concern that surgery with general anesthesia during a vulnerable period of infancy has an adverse effect on neurodevelopmental outcome and extends that concern to VLBW neonates. On the other hand, this analysis failed to demonstrate increased risk of NDI after surgical procedures that may have been performed under anesthesia other than general anesthesia.

The strengths of this study include the large, prospectively enrolled cohort of VLBW infants with individual assessments at 18–22 months' CA and adjustment for other risks. The major weaknesses are that the study is a retrospective cohort analysis for which the classification of surgery patients into subgroups is not confirmed by documented type of anesthesia, and there are potential confounders for which we were unable to adjust.

There have been no reported randomized control trials examining the potential adverse neurodevelopmental effects of general compared with spinal anesthesia for surgery, although at least one trial is underway for a selected procedure, inguinal herniorrhaphy.[52] It is currently not feasible, however, to conduct a trial of general versus non-general anesthesia for many procedures. Large retrospective analyses with extensive adjustment including for selection bias, using innovative approaches such as propensity scoring, may provide the best obtainable evidence that there are risks associated with general anesthesia and surgery in VLBW infants. Additional information is required about specific agents and the doses and duration of administration to determine if certain general anesthetic agents and/or practices carry greater risk and so should be avoided if alternatives are available. Meanwhile, potential neuroprotection strategies to ameliorate neurotoxicity may be investigated.[53, 54] Finally, postponement of elective procedures until young patients are older may be considered, especially if the procedure represents a second or subsequent anesthesia.

Conclusions

Exposure of VLBW infants to major surgery is associated with increased risk of death or NDI and of NDI among survivors, each by approximately 50%. The contribution of general anesthesia to this effect is suspected but not yet proven.

Supplementary Material

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Table 1

Characteristics of Subjects

Characteristic	Major Surgery[a] (n=2186)	Minor Surgery (n=784)	No Surgery (n=9141)	*P* Value
Birth year				
1998–2001, No. (column %)	667 (30.5)	314 (40.1)	3204 (35.1)	
2002–2005, No. (column %)	913 (41.8)	288 (36.7)	3506 (38.4)	<.001
2006–2009, No. (column %)	606 (27.7)	182 (23.2)	2431 (26.6)	
Birth weight, mean (SD), g	731.6 (143.2)	748.0 (146.5)	770.2 (158.4)	<.001
<500 g, No. (column %)	77 (3.5)	22 (2.8)	413 (4.5)	
500–999 g, No. (column %)	2055 (94.0)	741 (94.5)	8377 (91.6)	<.001
1000–1500 g, No. (column %)	54 (2.5)	21 (2.7)	351 (3.8)	
Gestational age, median (IQR), wk	25 (2)	25 (3)	26 (3)	<.001
<26 wk, No. (column %)	1347 (61.6)	395 (50.4)	4229 (46.3)	
26–28 wk, No. (column %)	765 (35.0)	320 (40.8)	4060 (44.4)	<.001
29–30 wk, No. (column %)	60 (2.7)	56 (7.1)	635 (7.0)	
>30 wk, No. (column %)	14 (0.6)	13 (1.7)	217 (2.4)	
Gender male, No. (column %)	1228 (56.2)	497 (63.4)	4364 (47.7)	<.001
Multiple birth cohort, No. (column %)	480 (22.0)	207 (26.4)	2,215 (24.2)	.02
Small-for-gestational-age, No. (column %)	274 (12.5)	146 (18.6)	1456 (15.9)	<.001
5-min Apgar score, median (IQR)	[n=2166] 7 (3)	[n=778] 7 (2)	[n=9030] 7 (2)	<.001
Caucasian, No./column total (%)	1171/2179 (53.7)	426/781 (54.5)	4832/9095 (53.1)	.69
Antenatal corticoid steroid exposure, No./column total (%)	1747/2174 (80.4)	641/781 (82.1)	7304/9118 (80.1)	.42
Postnatal corticosteroid exposure, No./column total (%)	717/2173 (33.0)	219/784 (27.9)	1292/9102 (14.2)	<.001
Severe intracranial hemorrhage and/or cystic periventricular leukomalacia, No./column total (%)	586/2182 (26.9)	163/773 (21.1)	1773/8610 (20.6)	<.001
Bronchopulmonary dysplasia, No./column total (%)	1294/1837 (70.4)	276/511 (54.0)	2452/6517 (37.6)	<.001
Sepsis and/or meningitis, No./column total (%)	1348/2184 (61.7)	368/781 (47.1)	2740/8295 (33.0)	<.001
Necrotizing enterocolitis, No./column total (%)	664/2184 (30.4)	282/784 (36.0)	389/9139 (4.26)	<.001
Patent ductus arteriosus, excluding those surgically closed, No./column total (%)	1047/2186 (47.9)	362/784 (46.2)	3366/9125 (36.9)	<.001
Seizures, No./column total (%)	333/2186 (15.2)	82/784 (10.5)	726/9137 (8.0)	<.001
Caregiver highest educational level:				
≤9 y, No./column total (%)	137/2009 (6.8)	58/672 (8.6)	628/8071 (7.8)	
10–12 y, No./column total (%)	302/2009 (15.0)	96/672 (14.3)	1,217/8071 (15.1)	

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Characteristic	**Major Surgery**[a] **(n=2186)**	**Minor Surgery (n=784)**	**No Surgery (n=9141)**	***P* Value**
>12 y, No./column total (%)	1156/2009 (57.5)	393/672 (58.5)	4671/8071 (57.9)	.55
Unknown, No./column total (%)	414/2009 (20.6)	125/672 (18.6)	1555/8071 (19.3)	

[a]With or without additional minor surgical procedure

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Table 2

Unadjusted Associations of Neurodevelopmental Outcomes with Patient Subgroups

Outcome	Major Surgery[a]	Minor Surgery	No Surgery	*P* Value
Death or neurodevelopmental impairment, column No./column total (%)	1401/2186 (64.1)	480/784 (61.2)	4364/9141 (47.7)	<.001
Neurodevelopmental impairment, column No./column total (%)	818/1603 (51.0)	179/483 (37.1)	1541/6318 (24.4)	<.001
BSID II MDI, mean (SD)	[n=1109] 71.3 (18.0)	[n=376] 77.0 (17.2)	[n=4525] 82.3 (17.4)	<.001
BSID II PDI, mean (SD)	[n=1109] 74.2 (19.3)	[n=372] 80.4 (17.5)	[n=4504] 87.1 (16.8)	<.001
BSID III Cognitive composite score, mean (SD)	[n=469] 82.7 (15.8)	[n=103] 88.9 (11.9)	[n=1771] 92.2 (14.0)	<.001
GMFCS ≥ 2, column No./column total (%)	242/1602 (15.1)	30/482 (6.2)	194/6313 (3.1)	<.001
Cerebral palsy, moderate or severe, column No./column total (%)	238/1600 (14.9)	32/482 (6.6)	198/6311 (3.1)	<.001
Blindness, column No./column total (%)	84/1600 (5.3)	4/481 (0.8)	24/6310 (0.4)	<.001
Deafness, column No./column total (%)	112/1597 (7.0)	12/482 (2.5)	155/6302 (2.5)	<.001

BSID II- Bayley Scales of Infant Development, Second Edition; BSID III - Bayley Scales of Infant Development, Third Edition; GMFCS – Gross Motor Function Classification System; MDI – Mental Developmental Index; PDI – Psychomotor Developmental Index

[a]With or without additional minor surgical procedure

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Table 3

Model 1: Multivariable Logistic Regression Analysis of the Primary Outcome Death or Neurodevelopmental Impairment with Two-Level Surgery Predictor Variable

Variable[a]	Adjusted Odds Ratio		
	Estimate	95% CI	
Surgery vs no surgery	1.29	1.08	1.55
Number of surgeries (for each additional surgery)	1.23	1.13	1.34
Birth weight (for each 250 g increase in weight)	0.70	0.60	0.81
Small-for-gestational-age	1.35	1.17	1.56
Male	1.63	1.42	1.88
Multiple birth cohort	1.30	1.15	1.48
Caucasian	0.75	0.67	0.84
5-min Apgar score ≤ 3	1.22	1.00	1.49
Antenatal corticosteroid exposure	0.84	0.72	0.98
Postnatal corticosteroid exposure	1.64	1.38	1.95
Seizures	2.93	2.31	3.71
Severe intracranial hemorrhage and/or cystic periventricular leukomalacia	2.12	1.78	2.54
Bronchopulmonary dysplasia (supplemental O2 at 36 wk)	1.47	1.25	1.72
Sepsis and/or meningitis	1.26	1.07	1.49
Necrotizing enterocolitis (Bell stage ≥ IIA)	1.26	0.83	1.92
Patent ductus arteriosus, excluding surgically closed patients	1.07	0.95	1.21
Caregiver highest educational level:			
10–12 y vs ≤9 y	0.86	0.69	1.07
>12 y vs ≤9 y	0.62	0.51	0.76
Birth year:			
2002–2005 vs 1998–2001	1.26	1.10	1.43
2006–2009 vs 1998–2001	0.64	0.55	0.76
Inborn	0.77	0.62	0.95
Propensity score- surgery[b] AOR per 10% increase in the predicted probability	1.02	0.92	1.14

[a]Neonatal Research Network center variable is also included in the model.

[b]Included in the PS model were BW, SGA, sex, race, 5-minute Apgar score, ICH, BPD, sepsis and/or meningitis, NEC, PDA, multiple birth cohort, antenatal corticosteroid exposure (ANS), PNS, highest level of education attained by primary caregiver, birth year, and center.

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Table 4

Model 3: Multivariable Logistic Regression Analysis of the Primary Outcome Death or Neurodevelopmental Impairment with Three-Level Surgery Predictor Variable

Variable[a]	**Adjusted Odds Ratio**		
	Estimate	**95% CI**	
Major surgery vs no surgery	1.52	1.24	1.87
Major surgery vs minor surgery	1.45	1.14	1.85
Minor surgery vs no surgery	1.05	0.83	1.33
Number of surgeries (for each additional surgery)	1.17	1.07	1.28
Birth weight (for each 250 g increase in weight)	0.73	0.63	0.85
Small-for-gestational-age	1.45	1.25	1.68
Male	1.74	1.49	2.03
Multiple birth cohort	1.33	1.18	1.51
Caucasian	0.73	0.65	0.82
5-min Apgar score ≤ 3	1.17	0.96	1.42
Antenatal corticosteroid exposure	0.84	0.72	0.98
Postnatal corticosteroid exposure	1.63	1.37	1.93
Seizures	2.88	2.27	3.65
Severe intracranial hemorrhage and/or cystic periventricular leukomalacia	1.99	1.68	2.37
Bronchopulmonary dysplasia (supplemental O2 at 36 wk)	1.41	1.21	1.64
Sepsis and/or meningitis	1.18	1.02	1.38
Necrotizing enterocolitis (Bell stage ≥ IIA)	1.12	0.76	1.65
Patent ductus arteriosus, excluding surgically closed patients	1.09	0.96	1.22
Caregiver highest educational level:			
10–12 y vs ≤9 y	0.86	0.69	1.08
>12 y vs ≤9 y	0.62	0.51	0.76
Birth year:			
2002–2005 vs 1998–2001	1.18	1.03	1.36
2006–2009 vs 1998–2001	0.60	0.50	0.71
Inborn	0.77	0.63	0.95
Propensity score[b], minor surgery AOR per 10% increase in the predicted probability	0.88	0.72	1.07

Variable[a]	Adjusted Odds Ratio		
	Estimate	**95% CI**	
Propensity score[b], major surgery AOR per 10% increase in the predicted probability	1.07	0.98	1.18

[a]Neonatal Research Network center variable is also included in the model.

[b]Included in the PS model were BW, SGA, sex, race, 5-minute Apgar score, ICH, BPD, sepsis and/or meningitis, NEC, PDA, multiple birth cohort, ANS, PNS, highest level of education attained by primary caregiver, birth year, and center.

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Table 5

Models 5 and 6: Multivariable Linear Regression Analyses for Mean BSID II MDI and Mean PDI with Three-Level Surgery Predictor Variables

	Model 5 for Mean Mental Developmental Index			Model 6 for Mean Psychomotor Developmental Index		
Variable[a]	**Estimate**	**95% CI**		**Estimate**	**95% CI**	
No surgery vs major surgery	3.3	1.4	5.1	3.6	1.8	5.4
Minor surgery vs major surgery	3.6	1.5	5.3	3.1	1.0	5.2
No surgery vs minor surgery	−0.3	−2.3	1.6	0.5	−1.5	2.5
Number of surgeries (for each additional surgery)	−0.9	−1.6	−0.1	−1.5	−2.3	−0.7
Birth weight (for each 250 g. increase in weight)	3.4	2.2	4.5	2.1	0.9	3.2
Small-for-gestational-age (no vs yes)	1.9	0.7	3.1	3.5	2.3	4.7
Male (no vs yes)	6.1	4.9	7.2	3.9	2.8	5.1
Multiple birth cohort (no vs yes)	3.0	2.0	4.0	2.3	1.3	3.3
Caucasian (yes vs no)	5.1	4.2	6.0	−0.4	−1.3	0.5
5-min Apgar score ≤ 3 (no vs yes)	1.5	−0.2	3.2	1.0	−0.7	2.7
Antenatal corticosteroid exposure (yes vs no)	1.2	−0.04	2.4	1.3	0.090	2.52
Postnatal corticosteroid exposure (no vs yes)	1.9	0.6	3.2	3.27	2.0	4.6
Seizures (no vs yes)	7.5	5.5	9.5	8.4	6.4	10.4
Severe intracranial hemorrhage and/or cystic periventricular leukomalacia (no vs yes)	5.1	3.7	6.5	9.1	7.7	10.5
Bronchopulmonary dysplasia (no vs yes)	2.4	1.2	3.6	3.1	1.9	4.3
Sepsis and/or meningitis (no vs yes)	1.3	0.1	2.5	0.9	−0.3	2.1
Patent ductus arteriosus, excluding surgically closed patients (no vs yes)	1.2	0.3	2.18	1.0	0.02	1.9
Necrotizing enterocolitis (Bell stage ≥ IIA) (no vs yes)	0.6	−2.2	3.5	0.2	−2.6	3.1
Caregiver highest educational level:						

	Model 5 for Mean Mental Developmental Index			Model 6 for Mean Psychomotor Developmental Index		
Variable[a]	**Estimate**	**95% CI**		**Estimate**	**95% CI**	
10–12 y vs ≤9 y	2.9	1.1	4.7	1.1	−0.7	2.9
>12 y vs ≤9 y	7.0	5.4	8.5	2.6	1.1	4.2
Birth year, 1998–2001 vs 2002–2005	0.5	−0.4	1.5	−0.1	−1.03	0.9
Inborn (yes vs. no)	1.8	0.2	3.4	1.2	−0.4	2.9
Propensity score[b], minor surgery AOR per 10% increase in the predicted probability	1.0	−0.4	2.3	1.2	−0.1	2.6
Propensity score[b], major surgery AOR per 10% increase in the predicted probability	−0.5	−1.2	0.3	−0.4	−1.1	0.3

[a]Neonatal Research Network center variable is also included in the models.

[b]Included in the PS model were BW, SGA, sex, race, 5-minute Apgar score, ICH, BPD, sepsis and/or meningitis, NEC, PDA, multiple birth cohort, ANS, PNS, highest level of education attained by primary caregiver, birth year, and center.

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