Published in final edited form as:

Paediatr Anaesth. 2014 March ; 24(3): 266–274. doi:10.1111/pan.12350.

The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study

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Summary

Background—Adverse neurodevelopmental outcomes are observed in up to 50% of infants after complex cardiac surgery. We sought to determine the association of perioperative anesthetic exposure with neurodevelopmental outcomes at age 12 months in neonates undergoing complex cardiac surgery and to determine the effect of brain injury determined by magnetic resonance imaging (MRI).

Methods—Retrospective cohort study of neonates undergoing complex cardiac surgery who had preoperative and 7-day postoperative brain MRI and 12-month neurodevelopmental testing with

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Doses of volatile anesthetics (VAA), benzodiazepines, and opioids were determined during the first 12 months of life.

Results—From a database of 97 infants, 59 met inclusion criteria. Mean $\pm$ SD composite standard scores were as follows: cognitive = 102.1 ± 13.3 , language = 87.8 ± 12.5 , and motor = 89.6 ± 14.1 . After forward stepwise multivariable analysis, new postoperative MRI injury ($P = 0.039$) and higher VAA exposure ($P = 0.028$) were associated with lower cognitive scores. ICU length of stay (independent of brain injury) was associated with lower performance on all categories of the Bayley-III ($P < 0.02$).

Conclusions—After adjustment for multiple relevant covariates, we demonstrated an association between VAA exposure, brain injury, ICU length of stay, and lower neurodevelopmental outcome scores at 12 months of age. These findings support the need for further studies to identify potential modifiable factors in the perioperative care of neonates with CHD to improve neurodevelopmental outcomes.

Keywords

congenital heart disease; neonate; neurodevelopment; inhaled agents; intravenous agents; general anesthesia

Background

Congenital heart disease (CHD) is present in 7–9 per 1000 births in Europe, Asia, and North America, and approximately 25% require surgery in the first year of life (1,2). Perioperative survival in neonates undergoing cardiac surgery is now >90% in most parts of the world, and neurodevelopmental outcomes have become the focus of significant research efforts (1,3-5). Thirty to fifty percent of neonates undergoing complex open heart surgery experience problems with general intelligence, receptive and expressive language, and gross and fine motor functioning when tested during infancy (6). At the age of school entry, deficits in cognition, language, visual-motor integration, reading, mathematics, executive function, and memory are also significantly more frequent than in the general population (7,8). Associations with worse neurodevelopmental outcomes include structural brain immaturity (9-11), magnetic resonance imaging (MRI) brain injury (12), chromosome anomalies (13), cardiac lesions with a single functional ventricle (7), prolonged deep hypothermic circulatory arrest (DHCA) (11,14), extreme hemodilution during bypass (15), and low regional cerebral oxygen saturation (rSO₂) in the perioperative period (16). Despite significant new insights over the past decade into the multiple perioperative causes of these adverse neurodevelopmental outcomes (i.e., specific cardiac lesion, duration of surgery, duration of aortic cross-clamping), statistical models explain well less than half of the variation in neurodevelopmental scores (7,17,18); these outcomes have not changed significantly over time (19). Furthermore, many of the identified factors associated with lower neurodevelopmental scores are not modifiable (i.e., brain immaturity, parental education and intelligence, and cardiac diagnosis) (7,18,20).

New brain lesions on MRI of infants undergoing cardiac surgery are prevalent without overt neurologic deficits (21). This implies that a large number of infants with CHD undergo

operative and perioperative management with unrecognized brain injuries. The impact of many perioperative care decisions (i.e., sedative/analgesic selection, rehabilitation, early oral feeding, care protocols) on neurodevelopmental outcomes is unknown in this high-risk population. For instance, infants with CHD experience significant anesthetic and sedative agent exposure before, during, and after their multiple operative/diagnostic procedures, which has potential implications for neurodevelopment and recovery from acute brain injury.

Neuroplasticity and neuroapoptosis, important processes in normal neurodevelopment and recovery, are potentially influenced by the effects of gamma-aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) binding by anesthetic and sedative agents with both positive and negative effects in various animal and *in vitro* models (22-24). While discussions are ongoing about the relationship between anesthetic exposure in infancy and long-term neurodevelopmental and behavioral problems (25-28), the association between perioperative exposure to anesthetic/sedatives and neurologic outcomes in infant CHD repair is largely unexplored (29). In this study, we sought to determine the association of perioperative brain injury and cumulative anesthetic and sedative exposure with 12-month neurodevelopmental outcomes in a cohort of neonates undergoing complex cardiac surgery with cardiopulmonary bypass. We hypothesized that brain injury and perioperative anesthetic agent exposure would be associated with lower neurodevelopmental scores after adjustment for additional important covariates.

Methods

The Baylor College of Medicine Institutional Review Board approved this retrospective cohort study. The study database was composed of prior prospective studies at our institution (12,17,21,30-32). Using this database, a retrospective cohort of neonates with CHD was identified based on the presence of preoperative and 7-day postoperative brain MRI and survival to completion of 12-month neurocognitive evaluations. Criteria for inclusion in the database were as follows: (i) enrollment into a prospective study at our institution, (ii) neonates (<30 days) scheduled for cardiac surgery with hypothermic cardiopulmonary bypass (CPB) for >60 min; and (iii) anatomic lesions that categorized patients as follows: single ventricle lesions: hypoplastic left heart syndrome or variant undergoing Norwood stage I palliation; or two-ventricle lesions: D-transposition of the great vessels undergoing arterial switch operation; interrupted aortic arch with ventricular septal defect; or other complete two-ventricle anatomic repair including truncus arteriosus, tetralogy of Fallot, or total anomalous pulmonary venous return.

Exclusion criteria for database enrollment were as follows: (i) gestational age <35 weeks at birth; (ii) weight <2.0 kg; (iii) known recognizable dysmorphic syndrome; (iv) surgery not requiring CPB; or (v) preoperative cardiac arrest. Intraoperative factors that resulted in exclusion were cases where aortic cross-clamping was not used, CPB times were anticipated to be <60 min, and a nadir temperature on bypass >30°C was planned. Of note, previous publications from studies contributing to this database neither used this specific cohort nor did they include the current retrospective study variable of cumulative perioperative anesthetic and sedative agent exposure.

Intraoperative parameters included in the database were related to the anesthetic, surgical, and CPB techniques for the neonatal cardiac surgery and have been reported in detail previously (21). Briefly, anesthetic technique for the neonatal surgery was standardized and consisted of isoflurane, fentanyl, and midazolam. Bypass flow rates of $150 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ were utilized, and pHstat blood gas management was used for all cases. When aortic arch reconstruction was planned, regional cerebral perfusion (RCP) was utilized at 18°C , with cooling over no $<20 \text{ min}$ (21). Hematocrit was maintained at 30–35% during cooling and hypothermic periods and increased to 40–45% during rewarming. rSO_2 was monitored throughout the perioperative period with a protocol that attempted to maintain $\text{rSO}_2 >50\%$ before and after bypass and $>90\%$ while on bypass (INVOS 5100B; Somanetics, Inc., Troy, MI, USA) (21). Chromosome analysis was performed by chromosomal microarray, or fluorescence *in situ* hybridization analysis, when a genetic syndrome was suspected. Inotrope score was recorded at 24, 48, and 72 h after the neonatal surgery to assess hemodynamic status (33).

Perioperative anesthetic and sedative data for the intraoperative period and the first 72 h after the primary surgery were already part of the database and had been collected prospectively as part of past studies. Outside the primary surgery, a retrospective chart review was conducted to collect all possible volatile anesthetic agent (VAA) and intravenous anesthetic agent (IAA) exposure in the first 12 months of life. This included all subsequent anesthetics (cardiac and noncardiac surgeries and cardiac catheterizations), procedural sedations, and additional hospital admissions. The following sources for the retrospective chart review were utilized: anesthetic records, perfusion records, intensive care unit nursing flow sheets, medication administration records, and pharmacy drug administration databases. Doses and times of administration were cross-checked to eliminate duplicate entries. After the initial data collection (HBA, MRM), all medication administration was rechecked to ensure accuracy of final data (TH, CH, RBE).

Volatile anesthetic agent (VAA) data were collected from both the anesthetic and perfusion records to account for the entire operative period. Endtidal anesthetic concentration (isoflurane and sevoflurane/desflurane if utilized after the neonatal surgery) was recorded at 5- to 15-min intervals from handwritten or electronic anesthesia records and converted into age-adjusted minimum alveolar concentration-hours (MAC-hours) (34,35) using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Additional VAA exposure from the CPB sweep gas inspired concentration was recorded every 5–10 min, and MAC-hours calculated. Opioid exposure was converted into fentanyl equivalents using the following formula: fentanyl $10 \mu\text{g} = \text{morphine } 1 \text{ mg} = \text{methadone } 1 \text{ mg}$ (36). Benzodiazepine equivalents were calculated by adding midazolam doses and lorazepam doses in milligrams. All other drug classes (dexmedetomidine, ketamine, chloral hydrate) were calculated separately. Propofol administration was used in a single patient and therefore was not quantified. All drug doses were divided by the patient's weight in kilogram at the time of administration.

Brain magnetic resonance imaging (MRI) under general endotracheal anesthesia was obtained immediately preoperatively and 7-days postoperatively, around the initial surgery. MRI was performed on a 1.5 Tesla Intera scanner (Philips Medical Systems, Best, the Netherlands), including standard T1, T2, diffusion-weighted imaging, and susceptibility-

weighted imaging (21). All MRIs were evaluated by pediatric neuroradiologists unaware of diagnosis or surgery. Abnormalities were classified as follows: white matter injury, intraparenchymal infarction, or intraparenchymal or intraventricular hemorrhage. MRI injury definitions and grading scale have been described in detail previously; all injuries were classified as mild, moderate, or severe (21). MRI injuries were designated as either preoperative or new postoperative brain injury and analyzed separately. In addition to the assessment of structural brain injury, a brain total maturity score (TMS) was used to assess structural maturity of the brain for the preoperative MRI (37).

Neurodevelopmental testing was performed using the Bayley Scales of Infant and Toddler Development, Third Edition (PsychCorp.-Harcourt, Brace, & Co., San Antonio, TX, USA, 2006), at 12 months of age (Bayley-III). The Bayley-III produces three primary composite standard scores, the cognitive, motor, and language composite scores, measured by performance of specified tasks, scored against a normative population, and scaled to have a mean score of 100 with a standard deviation of 15. These tests were administered by a single developmental psychologist (MT) unaware of diagnosis or surgery performed. Maternal intelligence was evaluated using the Wechsler Abbreviated Scale of Intelligence (PsychCorp.-Harcourt, Brace, & Co., 1999).

Statistics

Patients who survived and returned for the 12-month neurodevelopmental assessment were included in the analysis. Continuous variables with normal distribution are reported as mean $\pm$ standard deviation and were compared with unpaired two-sided *t*-test. Non-normally distributed continuous variables are reported as median (25th–75th percentile range) and compared with the Mann–Whitney *U* test. Discrete variables are reported as median (25th–75th percentile range) and compared with the Mann–Whitney *U* test.

Forward stepwise multivariable regression was performed to assess the association of perioperative anesthetic exposure and MRI brain injury with 12-month cognitive, language, and motor composite standard scores. A total of 22 covariates were first assessed by univariate linear regression analysis: birth weight, gestational age, single- versus two-ventricle cardiac lesions, total bypass, regional cerebral perfusion, and deep hypothermic circulatory arrest times for all cardiac surgeries in the first 12 months; mean preoperative, intraoperative, and 72-h postoperative rSO_2 , for the neonatal cardiac surgery; mean inotrope score for the first 72 h of the neonatal surgery; total ICU and hospital length of stays for the first 12 months; presence of a chromosome abnormality, maternal IQ, MRI brain maturity score, and erythropoietin and aprotinin administration. In addition, total opioid, benzodiazepine, and VAA exposure in the first 12 months were assessed. Finally, the presence of a preoperative MRI brain injury and occurrence of a new postoperative MRI brain injury were assessed as separate covariates. After univariate analysis, all covariates with a *P* value of <0.10 were included in the forward stepwise multivariable analysis. Covariates for anesthetic exposure and MRI brain injury were forced into the final models. Assessment of variance inflation factor for the final models was performed to exclude multicollinearity. Covariates having coefficients with *P* values <0.05 and 95% confidence intervals excluding zero were considered significant associations in the final model. R-

squared and adjusted R-squared values were calculated for each model, to report the proportion of variation of each domain on the Bayley-III explained by the model. A *post hoc* power analysis to exclude type I error with an alpha value of 0.05 was performed for each multivariable model.

Results

From the database, 97 neonates underwent pre- and postoperative brain MRI evaluations; four subjects did not receive the intended surgery with CPB and were excluded from further analysis. Of these 93 subjects, 10 died in the first 12 months of life (none in the immediate postoperative period), and 24 did not return for further testing, leaving 59 subjects (71% of survivors) returning for the 12-month neurodevelopmental testing. The entire study cohort underwent retrospective chart review for perioperative VAA and IAA exposures (Figure 1). Patient characteristics are displayed in Table 1. Eighteen (31%) subjects had preoperative MRI brain injury, and 28 (47%) experienced a new postoperative MRI brain injury. The details of the time relative to surgery, type, and severity of MRI brain injuries are reported in Table 2. Figure 2 demonstrates typical MRI brain injury pattern in this cohort.

All subjects received perioperative VAA and IAA. VAA included all inhalational agents (isoflurane, sevoflurane, and desflurane). Other drugs included ketamine, dexmedetomidine, chloral hydrate, opioids, and benzodiazepines. All subjects (100%) received opioids and benzodiazepines, while <35% received other IAA. Because only a small percentage of subjects received ketamine, propofol, dexmedetomidine, barbiturates, or chloral hydrate during the first 12 months of life and exposure to these agents was typically small, they were not included in the multivariable analysis.

Composite standard scores for the entire 59 subjects were as follows: cognitive = 102.1 ± 13.3 , language = 87.8 ± 12.5 , and motor = 89.6 ± 14.1 . The final forward stepwise multivariable models are displayed in Table 3. There were no missing data among all the covariates and outcomes tested. The most consistent association was between longer ICU length of stay and lower Bayley-III scores, in all three directly measured domains. For every 10 days in the ICU, there was an associated decrease of 4.8, 4.1, and 3.5 points on each respective section of the 12-month Bayley-III cognitive, language, and motor scores. In addition, increasing VAA exposure demonstrated a significant association with lower cognitive scores ($P = 0.028$), and new postoperative MRI brain injury was associated with lower cognitive ($P = 0.039$) and language ($P = 0.020$) scores. There was an association of larger fentanyl doses with higher cognitive and language scores and larger benzodiazepine doses with higher cognitive scores; the effect size of these associations was small. Other associations with lower Bayley-III scores were lower preoperative rSO_2 (cognitive and motor), aprotinin use (language), and abnormal chromosomes (motor and language). Using adjusted R^2 , the final models explained 23–33% of the variability in Bayley-III scores. The power of the models to exclude type I error with alpha value of 0.05 was 96–99%.

Discussion

This study, to our knowledge, is the largest to date to report complete data on perioperative MRI brain injury and cumulative anesthetic agent exposure during the first 12 months of life and their potential association with neurodevelopmental outcomes in a cohort of neonates undergoing complex congenital heart surgery. After adjustment for multiple covariates previously demonstrated or suspected to influence neurodevelopmental outcomes in this population, we demonstrated that larger exposure to VAA and the presence of a new postoperative MRI brain injury were associated with lower Bayley-III cognitive composite scores and a trend ($P = 0.056$) for lower language scores. The most consistent association with lower neurodevelopmental outcomes was longer total length of ICU stay in the first 12 months, with all three domains on the Bayley-III.

Guerra *et al.* (29) also reported the neurodevelopmental outcomes of neonates undergoing complex open heart surgery in the first 6 weeks of life. These authors studied 93 patients and also used the Bayley Scales of Infant Development examination of neurodevelopment; however, they changed the evaluation tool mid-study from version II ($n = 45$) to version III ($n = 48$). Because of this change, the authors only reported associations with severe delays (>2 SD below test population normal means, or <70). Even though the Bayley was administered at 18–24 months, the VAA and intravenous anesthetic and sedative data were only collected for the first 6 weeks of life. These authors found no association between exposure to any class of anesthetic or sedative agent and significant neurodevelopmental delay. In a follow-up study of this same cohort tested at 4 years of age, 91 subjects were administered tests for full scale IQ, performance IQ, verbal IQ, visual-motor integration, and adaptive behavior. Increasing days of postoperative ventilation was the most consistent risk factor, exhibiting a significant association with lower scores in all domains. Small associations were demonstrated between greater number of days receiving chloral hydrate and lower performance IQ, and larger benzodiazepine dose and visual-motor integration (38).

An important finding of our study is documentation of the large exposure of our patient population to VAA, opioids, and benzodiazepines during the first 12 months. Our patient cohort had a mean VAA exposure over 4 MAC-hours in the first year of life, with a range of <0.5 to 15 MAC-hours; five of the 59 patients had 10–15 MAC-hours of exposure. The bulk of this exposure occurred in the neonatal period, which is the time of most rapid synaptogenesis and brain growth (28). Significantly increased VAA exposure combined with documented brain injury in our cohort partially explains the associations found in our study. Even though there are a variety of risk factors affecting neurodevelopment in CHD neonates, VAA exposure should be recognized as both a potential contributor and a modifiable exposure in the perioperative period. This presents an opportunity for future research to alter anesthetic techniques and doses, for example, reduced VAA exposure. Different drug classes without neuroapoptotic effects in animal models such as the α_2 agonists clonidine and dexmedetomidine could be studied (39).

The potential confounding factors in our patient cohort are significant and include those previously mentioned: bypass techniques, cardiac diagnosis, cerebral oxygen desaturation,

intercurrent events such as cardiac arrest and extracorporeal membrane oxygenation, and medical illnesses. Chromosome anomalies and parental intelligence are also important factors. These issues make definitive determination of the effect of anesthetic and sedative exposure on neurodevelopment difficult. Longer ICU length of stay has consistently been demonstrated as a risk factor for lower neurodevelopmental outcomes after infant cardiac surgery; we did demonstrate that this factor was the most consistent association in our cohort (18,29,38). We attempted to adjust for as many of these factors as possible. We did not demonstrate an effect of birthweight or gestational age, bypass duration, intra- or postoperative rSO₂, erythropoietin administration, or inotrope score with neurodevelopmental outcomes. Additionally, only a new postoperative MRI brain injury was associated with lower neurodevelopmental scores; a preoperative MRI brain injury was not.

There are several important limitations to this study. During CPB, the perfusionists recorded inspired anesthetic gas concentrations from the vaporizer dial; because of the low sweep gas flow and known limited diffusion of anesthetic gas into the blood across CPB membrane oxygenators (40), the VAA exposure may be overestimated. Endtidal or inspired VAA concentration does not indicate brain concentration of these agents, and thus, the true exposure of the vulnerable end organ of interest is not known. Finally, the Bayley-III at the age of 12 months has limited predictive ability for neurodevelopmental outcomes at later ages (41); generally, at the age of 4 years and older, it is possible to test additional domains of intelligence and development, including reading, mathematics, memory, and executive functions. Therefore, lower scores in this cohort at the age of 12 months may not translate to lower scores by age at school entry, which generally has much better predictive ability for later school performance and achievement. The current cohorts are being formally tested through age 5 years as part of the original research protocols.

Conclusions

In this study, we demonstrate an association between perioperative anesthetic exposure, MRI brain injury, and neurodevelopmental outcome scores using the Bayley-III at the age of 12 months. Larger VAA exposure and new postoperative brain injury on MRI were associated with lower neurodevelopmental scores. Ultimately, the duration of ICU stay, with or without brain injury, was most strongly associated with poor neurocognitive outcome assessed with a 12-month Bayley-III. These preliminary findings support the need for further study on how recovery from perioperative brain injury in neonates with CHD may be influenced by modifiable elements of the ICU environment and clinical care (such as VAA and IAA treatment) that could potentially impact ICU length of stay and neurocognitive outcomes.

Acknowledgments

This study was approved by the Institutional Review Board of the Baylor College of Medicine. Informed written consent from parent or guardian was obtained for all studies represented in the database.

Funding

This work was supported by United States National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Development Grant (Grant Number 1R21-HD55501-01), Baylor College of Medicine General Clinical Research Center Grant #0942 funded by United States National Institutes of Health (Grant Number M01 RR00188), Charles A. Dana Foundation Brain and Immuno-Imaging Grant, and Texas Children's Hospital Anesthesiology Research Fund to DBA. This work was also supported by the Foundation for Anesthesia Education and Research's Medical Student Anesthesia Research Fellowship (Grant Number #01/01/2012) to HBA.

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Figure 1.
Patient enrollment.

Figure 2.

Representative perioperative MRI brain injury. Neonate with hypoplastic left heart syndrome born at 36-week gestation, birthweight 2620 g. Three-dimensional sagittal T1-weighted images, 1 mm slice thickness. (a,b): Preoperative scan at the age of 4 days. (a) Sagittal slice to right of midline with no white matter injury (WMI). (b) Sagittal slice to left of midline. WMI: two punctate T1 hyperintense foci in the left posterior temporal periventricular white matter. (Arrows) (c) Postoperative MRI at the age of 11 days, same slice (a). New WMI in frontal periventricular area. (Arrows) (d) Same slice (b). New WMI in left posterior temporal periventricular area. (Arrows) There is an immature appearance of the brain with diminished tertiary sulcation and very incomplete myelination. The brain total maturity score is 10. Brain maturity is representative of that observed with 34- to 35-week gestational age in infants without congenital heart disease.

Table 1Patient characteristics and clinical data, $n = 59$

Patient and genetic data	
Male, N (%)	34 (58)
Gestational age (weeks)	38.4 ± 1.2
Weight, g	3179 ± 503
Chromosome abnormality, N (%)	12 (20)
Maternal IQ	101.3 ± 16.1
TMS scores	11.7 ± 1.3
Cardiac diagnosis	
HLHS/other single ventricle, N (%)	28 (47)
D-transposition of the great arteries, N (%)	20 (33)
Aortic arch hypoplasia and other two-ventricle lesions, N (%)	12 (20)
Anesthetic, surgical, and hospital data	
Total number of anesthetic exposures (cardiac and noncardiac)	3 (2–4)
Total number of cardiac surgeries	2 (1–2)
Total CPB time of all surgeries (min)	266 ± 107
Total MAC-hour of exposure	4.4 ± 3.1
Total number of anesthetic agents (VAA + IAA)	5 (5–6)
Total number of IAA	4 (4–5)
Total fentanyl equivalents dose (ICU+OR), mcg/kg	553 ± 585
Total benzodiazepine equivalents dose (ICU+OR), mg/kg	14.3 ± 25.0
LOS ICU (days)	9 (7–12)
LOS hospital (days)	28 (21–48)
MRI brain injury data	
Preoperative MRI brain injury, N (%)	18 (31)
New postoperative MRI brain injury, N (%)	28 (47)
Neurodevelopmental outcome data	
12-month Bayley-III cognitive score	102.1 ± 13.3
12-month Bayley-III language score	87.8 ± 12.5
12-month Bayley-III motor score	89.6 ± 14.1

HLHS, hypoplastic left heart syndrome; VAA, volatile anesthetic agents; IAA, intravenous anesthetic agents; MAC-hour, minimum alveolar concentration-hour; ICU, intensive care unit; OR, operating room; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; LOS, length of stay; IQ, intelligence quotient; TMS, brain MRI total maturity score.

Normally distributed data expressed as mean $\pm$ standard deviation; non-normally distributed data expressed as median (25th–75th percentile).

Table 2Perioperative brain magnetic resonance imaging (MRI) findings, $N = 39$

Brain MRI results	Preoperative injury	New postoperative injury
Total with WMI, infarction, hemorrhage, N (%)	18 (46%)	28 (71%)
WMI, N (%)	12 (31%)	14 (36%)
WMI severity: mild/moderate/severe (N)	8/3/1	10/4/0
Infarction, N (%)	9 (23%)	10 (26%)
Infarction severity: mild/moderate/severe (N)	5/3/1	10/0/0
Hemorrhage, N (%)	4 (10%)	10 (26%)
Hemorrhage severity: mild/moderate/severe (N)	4/0/0	9/0/1

Brain injury type and severity in the 39 patients with pre- and/or post-operative MRI brain injury. Twenty patients had normal pre- and post-operative MRI scans and are not reported. New postoperative injury was defined as either a completely new lesion, or worsening of an existing lesion. Lesions diagnosed on the preoperative MRI that were unchanged, improved, or not observed on the postoperative MRI that were not designated as new postoperative MRI injury.

Abbreviation: WMI, white matter injury. Some patients had more than one type of injury, resulting in totals of WMI, infarction, hemorrhage in each group being greater than the total number of brain injured patients.

Table 3

Forward stepwise multivariable analysis final model of perioperative associations with Bayley Scales of Infant Development III cognitive, language, and motor composite scores at the age of 12 months

Covariate	Cognitive			Language			Motor		
	P value	Coefficient (95% CI)		P Value	Coefficient (95% CI)		P value	Coefficient (95% CI)	
Preoperative MRI injury ^a	0.548	-2.04 (-8.80, 4.72)		0.179	-4.15 (-10.27, +1.96)		0.390	-3.20 (-10.61, +4.21)	
NEW postoperative MRI injury ^a	0.030^b	-6.85 (-13.36, -0.34)		0.020^b	-6.96 (-12.79, -1.13)		0.053	-6.95 (-14.00, +0.10)	
MAC-hour VAA ^a	0.028^b	-1.26 (-2.37, -0.14)		0.056	-0.95 (-1.933, +0.03)		0.455	-0.47 (-1.71, +0.78)	
Fentanyl equivalents ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{y}^a$)	0.025^b	+0.01 (+0.01, +0.28)		0.007^b	+0.13 (+0.01, +0.02)		0.278	+0.01 (-0.01, +0.02)	
Benzodiazepine equivalents ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{y}^a$)	0.048^b	+0.14 (+0.01, +0.28)		0.643	-0.27 (-0.15, +0.09)		0.406	+0.06 (-0.09, +0.22)	
ICU LOS (d)	0.001^b	-0.48 (-0.75, -0.21)		0.001^b	-0.41 (-0.65, -0.17)		0.021^b	-0.35 (-0.64, -0.06)	
Preoperative mean rSO ₂ (%)	0.041^b	+0.45 (+0.02, +0.89)		-	-		0.018^b	0.59 (0.11, 1.07)	
Aprotinin administration	-	-		0.005^b	-8.26 (-13.85, -2.67)		-	-	
Abnormal chromosomes	-	-		0.031^b	-7.93 (-15.09, -0.75)		0.030^b	-9.79 (-18.60, -0.97)	
R ² of model	0.36			0.42			0.34		
Adjusted R ² of model	0.27			0.33			0.23		
Power of model with alpha = 0.050	0.99			0.99			0.96		

MRI, magnetic resonance imaging; MAC, minimum alveolar concentration; VAA, volatile anesthetic agents; ICU, intensive care unit; LOS, length of stay; rSO₂, regional cerebral oxygen saturation; CI, confidence interval, - no association in final model.

Additional covariates tested included birthweight, gestational age, single- versus two-ventricle cardiac lesion; maternal intelligence, hospital LOS, erythropoietin administration, MRI brain maturity score, bypass time, regional cerebral perfusion time, deep hypothermic circulatory arrest time, mean intraoperative and postoperative rSO₂, and mean inotrope score.

^a Covariates forced into final model.

^b Covariates with significant associations with Bayley Scales of Infant Development III neurodevelopmental testing domains (bold italic font).