HHS Public Access

Author manuscript

Anesthesiology. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Anesthesiology. 2023 October 01; 139(4): 393–404. doi:10.1097/ALN.0000000000004684.

Anesthesia and sedation exposure and neurodevelopmental outcomes in infants undergoing congenital cardiac surgery: a retrospective cohort study

Allan F. Simpao, MD, MBI[1,2,3], **Isabel R. Randazzo, BA**[4], **Jesse L. Chittams, MS**[5], **Nancy Burnham, CRNP, MSN**[4], **Marsha Gerdes, PhD**[6], **Judith C. Bernbaum, MD**[7], **Tia Walker, BS**[4], **Solveig Imsdahl, BA**[4], **Aaron G. DeWitt, MD**[1,7,8], **Elaine H. Zackai, MD**[7,9,10,11], **J. William Gaynor, MD**[4], **Andreas W. Loepke, MD, PhD**[1,2,12]

[1.]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA

[2.]Department of Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

[3.]Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia, Philadelphia, PA

[4.]Division of Cardiothoracic Surgery, Department of Surgery, Children's Hospital of Philadelphia and the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[5.]Biostatistics Consulting Unit, Office of Nursing Research, University of Pennsylvania School of Nursing, Philadelphia, PA

[6.]Department of Child and Adolescent Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, and the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[7.]Department of Pediatrics, Children's Hospital of Philadelphia, and the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[8.]Division of Cardiac Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, PA

[9.]Department of Obstetrics and Gynecology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[10.]Division of Pediatrics in Genetics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[11.]Division of Human Genetics and the Clinical Genetics Center at Children's Hospital of Philadelphia, Philadelphia, PA

[12.]Division of Cardiac Anesthesiology, Children's Hospital of Philadelphia, Philadelphia, PA

Corresponding Author: Allan F. Simpao, 3401 Civic Center Blvd., Philadelphia, PA, USA, Ph: 215-590-1000, simpaoa@chop.edu.

Clinical Trial Registration: Not applicable.

Prior Presentations: None.

Conflict of Interest: The authors declare no competing interests.

Abstract

Background: Children undergoing complex cardiac surgery are exposed to substantial cumulative doses of sedative medications and volatile anesthetics and are more frequently anesthetized with ketamine, compared with healthy children. We hypothesized that greater exposure to sedation and anesthesia in this population is associated with lower neurodevelopmental scores at 18-months of age.

Methods: We conducted a secondary analysis of infants with congenital heart disease who participated in a prospective observational study of environmental exposures and neurodevelopmental outcomes to assess the impact of cumulative volatile anesthetic agents and sedative medications. Cumulative minimum alveolar concentration hours of exposure to volatile anesthetic agents and all operating room and intensive care unit exposures to sedative and anesthesia medications were collected prior to administration of Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at 18-months of age.

Results: The study cohort included 41 (37%) single-ventricle and 69 (63%) two-ventricle patients. Exposures to volatile anesthetic agents, opioids, benzodiazepines and dexmedetomidine were not associated with abnormal Bayley-III scores. At 18-month follow-up, after adjusting for confounders, each mg/kg increase in ketamine exposure was associated with a 0.34 (95%CI: −0.64, −0.05) point decrease in Bayley-III Motor scores, P = 0.024.

Conclusions: Total cumulative exposures to volatile anesthetic agents were not associated with neurodevelopmental impairment in infants with congenital heart disease undergoing various imaging studies and procedures, whereas higher ketamine doses were associated with poorer motor performance.

Keywords

pediatrics; perioperative period; general anesthesia; congenital heart disease

Introduction

The past two decades have seen intense discussions about the potential long-term deleterious effects of anesthetic and sedative exposures in young children on brain development.[1,2] Dendritic and synaptic alterations, immature neuronal cell death and long-term impairment of memory, learning, and behavioral development have consistently been described in newborn animals, including non-human primates, for all clinically used γ-aminobutyric acid agonists and N-methyl-D-aspartate antagonists.[3,4] However, clinical studies in human infants and young children have not consistently demonstrated neurodevelopmental abnormalities following brief volatile anesthetic exposures for non-cardiac surgery and a randomized controlled trial and a well-designed ambi-directional cohort trial have found no cognitive abnormalities.[5,6,7] Importantly, however, exposure times in these clinical studies have largely been limited to less than 2 hours, while most animal studies have used exposures of 4 hours or more. While the existence and exact timing of a potential vulnerable period of the developing animal and human brain for the deleterious effects of anesthetic exposure remain controversial, it is generally felt that susceptibility may be highest in younger children and primates under 4-5 years of age.[1,2]

Neurodevelopmental disability is the most common complication for survivors of congenital cardiac surgery, and long-term studies in this vulnerable patient population have consistently reported significant cognitive and motor delays.[8,9,10] Children requiring cardiac surgery may be particularly susceptible to potentially deleterious effects of anesthetics and sedatives, as they frequently undergo prolonged procedures and sometimes multiple anesthetic exposures early in life, often within the neonatal period. Furthermore, children requiring cardiac surgery are frequently treated with sedative medications postoperatively, which due to their similar mechanism of action compared to volatile anesthetics may contribute to subsequent neurocognitive impairment.[11] Thus, we conducted a secondary analysis of the impact of exposure to volatile anesthetic agents and sedative medications in infants with congenital heart disease who were enrolled in a prospective observational study evaluating the relationship between environmental exposures and neurodevelopmental outcomes.[12] The primary aim of this analysis was to describe the association between neurodevelopmental outcomes and cumulative inpatient exposure to sedative and anesthetic medications during the first 18 months of life in children with congenital heart disease. The primary hypothesis was that greater exposure to sedation and anesthesia in infants undergoing cardiac surgery would be associated with lower neurodevelopmental scores at 18-month follow-up. A secondary aim was to examine and describe patterns of sedation and anesthesia administration in infants with congenital heart disease over the first 18 months of life.

Methods

Ethics Approval and Reporting Guidelines

The Children's Hospital of Philadelphia Institutional Review Board approved this study and waived the requirement for written informed consent. Informed consent was obtained for the parent study. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13]

Patient Population

This retrospective cohort study represents a secondary analysis of a prospective observational study evaluating environmental exposures and neurodevelopmental outcomes in pediatric patients with congenital heart disease undergoing surgery at Children's Hospital of Philadelphia, an urban, quaternary care pediatric hospital.[12] The prospective observational study did not include the retrospective study variables of cumulative in-hospital anesthetic and sedative agent exposures from birth until the neurodevelopmental evaluation at 18 months of age, which were therefore collected from medical and anesthetic records.

This study's inclusion and exclusion criteria were the criteria from the primary study, and the analysis plan was established before the data were accessed.[12] Inclusion criteria for this study included the following: infants with congenital heart disease necessitating surgery with cardiopulmonary bypass, date of surgery prior to 44 weeks post-conceptional age, biological parents of the infant with congenital heart disease necessitating surgery with cardiopulmonary bypass, and parental/guardian permission (informed consent). The inclusion criteria for the primary study specified biological parents because the study

involved trio whole exome sequencing. Exclusion criteria included a known genetic syndrome, a major extra-cardiac anomaly, and primary language other than English spoken in the home. Patients were evaluated by a genetic dysmorphologist. Neonatal recognition of dysmorphic features may be difficult; therefore, some patients for whom the diagnosis of a genetic syndrome was made at a later evaluation were enrolled. Genetic testing was performed as clinically indicated. Results of the genetic evaluations were classified as normal if no genetic or chromosome abnormality was demonstrated, abnormal if a specific diagnosis was confirmed, and suspect if there was evidence of a genetic syndrome that could not be confirmed.

Maternal education and the child's race were determined by parental report. Familial socioeconomic status was assessed by parental report according to the Hollingshead scale.[14]

Cardiac Diagnosis

Cardiac diagnosis was coded according to a previously described classification incorporating anatomy and perioperative physiology that has been shown to be predictive of perioperative mortality.[15] Class I represents 2 ventricles with no aortic arch obstruction, class II is 2 ventricles with aortic arch obstruction, class III is a single ventricle with no arch obstruction, and class IV is a single ventricle with arch obstruction. Accordingly, patients with tetralogy of Fallot and transposition of the great arteries are class I, for example, whereas patients with hypoplastic left heart syndrome represent class IV.

Follow-up Assessment at 18 Months

Medical follow-up included obtaining growth measurements and an interim medical history followed by a physical and neurological examination by a team of developmental pediatricians and a nurse practitioner. All patients underwent evaluation with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age.[16] The Bayley-III assesses development across five domains: cognition, language, motor, social-emotional and adaptive. The composite scores have a mean of 100 and a standard deviation of 15. The Bayley-III cognitive, language and motor composite scores were used as the primary outcomes for this study.

Measurements and Data Handling

The electronic health record and anesthesia information management system databases (CompuRecord, Philips, Andover, MA; Epic Systems Corporation, Verona, WI; ChartMaxx, Quest, Seacaucus, NJ) were queried to obtain the patient characteristics and intensive care unit and perioperative data for patients meeting the inclusion criteria. Data filtering and validation were performed to identify patients incorrectly classified as eligible patients and to exclude from analysis any patients who met the exclusion criteria. The authors performed manual chart review and data validation for every study patient. Exposure data including patient encounters, presence and absence of bolus and continuous infusions medication during encounters, continuous infusion calculations, and medication sum calculations were

audited at multiple timepoints over the course of the study. All audits demonstrated reliable data with error rates of 0% to 5%. The errors were corrected prior to statistical analysis.

Volatile anesthetic agent (halothane, sevoflurane, isoflurane, and desflurane) exposure data for all subjects' procedural and imaging encounters at our institution were retrieved from the anesthesia information management system and electronic health record databases (CompuRecord; Phillips Medical System, Andover, MA; Epic Anesthesia; Epic, Verona, WI) from the time of first anesthetic exposure to the date of neurodevelopmental assessment. All exposures to volatile anesthetic agents were recorded at intervals ranging from 15 seconds to 1 minute throughout each anesthesia encounter, with end-tidal exhaled volatile agent concentrations used for exposure calculations. Because volatile anesthetic agent administration is frequently continued until time of departure from the anesthetizing location, elimination assumptions were developed and used if the last recorded expired concentration of volatile anesthetic agent in the anesthetizing location was greater than zero so as to account for total volatile anesthetic agent exposure.[11] Specifically, end-tidal concentrations of all volatile anesthetic agents were assumed to drop by 50% at 5 minutes after cessation of administration. A concentration drop to 0 in 10 minutes was assumed for sevoflurane and desflurane, and a drop to 0 in 30 minutes was assumed for halothane and isoflurane.[11] Total volatile anesthetic agent exposure was then calculated and converted to age-adjusted minimum alveolar concentration hours (MAC-h).[17,18,19] Total volatile anesthetic agent exposure in cumulative MAC-h was then determined for each patient inclusive of all known anesthetic exposures prior to the developmental assessment at the 18-month follow-up visit, standardized and summed between different gases. Of note, end-tidal concentration for volatile anesthetic exposure during cardiopulmonary bypass could not be quantified and was therefore not included in this analysis.

Data on subjects' exposures to sedation, anesthesia, and opioid medications in the cardiac ICU were abstracted from electronic health record systems (ChartMaxx, Quest, Seacaucus, NJ; Epic). Each subject's daily weight was obtained to calculate weight-adjusted doses. Cardiac ICU exposures were tallied hourly and included boluses and continuous infusions of all sedatives, anesthetics, and analgesics given during hospital admissions before the 18-month follow-up assessment. Perioperative sedative exposures were also collected for all surgical procedures which occurred before the 18-month follow-up visit. All administered opioid doses of fentanyl, hydromorphone, demerol, oxycodone, and remifentanil were converted to weight-adjusted intravenous morphine equivalents.[20] All benzodiazepines including administered doses of midazolam, diazepam, and lorazepam were converted to weight-adjusted intravenous midazolam equivalent total doses.[21] For each patient, all doses were summed and weight-adjusted totals were generated for exposures of ketamine (mg/kg), dexmedetomidine (mcg/kg), opioids (mg/kg), and benzodiazepines (mg/kg) until the 18-month follow-up.

Statistical Analysis

There was no statistical power analysis conducted prior to the study. The intent was to recruit as many eligible patients as possible from the primary study to establish a representative sample; thus, the sample size was based on a convenience sample. The

primary outcomes of interest were the Bayley-III Motor, Language, and Cognitive scores. The primary exposures of interest included the following: exposures to volatile anesthetic agents, total operating room and ICU dexmedetomidine, total opioids, total benzodiazepines, and total ketamine. The patient characteristics considered as potential confounders included genetic anomaly, sex, race, mother's education level, socioeconomic class, need for extracorporeal membrane oxygenation (ECMO) therapy, birth weight z-score, and hospital length of stay.

Basic summary statistics were generated, as appropriate for the data, such as counts and percentages or means and standard deviations or median and interquartile range (IQR) for all primary outcomes, primary confounders, and patient characteristics. These were followed by scatter plots and bivariate analysis between each combination of outcome and independent variable. The bivariate analyses utilized Spearman correlations for continuous variables and Chi-square or Fisher's exact test, as applicable, for categorical variables. Lastly, general linear models were run to assess the effect of each primary exposure of interest on each primary outcome of interest while adjusting for potentially confounding patient characteristics, with and without statistical outliers. Separate regressions were run for each primay drug exposure of interest and each outcome. Any observation beyond the 99.7% confidence limits was considered a statistical outlier. Two-sided p-value < 0.05 was used as the criterion for statistical significance, and all results were considered exploratory. The data analysis was performed using SAS software version 9.4 (Cary, NC, USA).[22]

Results

Of the 140 patients enrolled in the initial study, 10 patients died and 20 were lost to follow up and excluded from the primary study. All patients in the primary study met the inclusion criteria for this study. Thus, the primary study's cohort and this study's cohort consisted of 110 patients enrolled between September 1, 2011, and August 31, 2015, who completed neurodevelopmental evaluations at the 18-month follow up visit. Table 1 summarizes the demographic and clinical characteristics of the study cohort and patients who were alive yet lost to follow-up ("live non-returners").[12] The median birth weight was 3.3 kg (IQR: 3.0 – 3.6 kg). 91 subjects were admitted on the first day of life and the remaining 19 subjects at ages 2 to 11 days. Median length of stay was 15 days (IQR: 11 – 23 d). The cohort included 41 (37%) single-ventricle patients and 69 (63%) two-ventricle patients.

Table 2 shows the counts and percentages of patients exposed to sedation and anesthesia at the 18-month follow-up visit. Weight-adjusted anesthetic and sedative exposures at 18-month follow-up are listed in Table 3. During the first hospitalization, infants received at least 1 anesthetic or sedative drug for a median of 12 days (IQR: 9 – 19 d), which on average comprised 81% (95% CI: 77%, 84%) of the initial length of stay. Concurrent administration of 2 or more sedative agents (i.e., polypharmacy) in the intensive care unit occurred for a mean 38% (95% CI: 34%, 42%) of the initial length of stay. By the 18-month follow-up, over half of the study cohort had been exposed to two or more of the following agents: volatile anesthetic, fentanyl, ketamine, morphine, oxycodone, pentobarbital, midazolam, and dexmedetomidine. When compared to patients with two ventricles, single-ventricle patients had been exposed to polypharmacy to a greater degree at 18-month follow-up (Table 2),

and single-ventricle patients received higher doses across all anesthetic and sedative agents (Supplemental Table 1).

Bayley-III Motor, Cognitive and Language scores at the 18-month follow-up visit for the entire study cohort and grouped by cardiac class are shown in Table 4. The Bayley-III Motor, Cognitive and Language scores for subjects who did not receive ECMO (n=107) were 92.7 ± 1.1, 94.0 ± 1.1, and 92.9 ± 1.7, respectively, while the Bayley-III Motor, Cognitive and Language scores for those needing ECMO (n=3) were 66.3 ± 6.3, 65.0 ± 6.8, and 59.0 ± 10.0, respectively. Two-ventricle patients (cardiac classes I and II, n = 69) had significantly higher Bayley-III Motor scores than single-ventricle patients (cardiac classes III and IV, n = 41) (94.4 ± 9.3, 87.8 ± 14.0; $P = 0.004$), while Bayley-III Cognitive and Language scores did not significantly differ across the two-ventricle and single-ventricle groups (Cognitive, two-ventricle: 94.3 ± 11.1, single ventricle: 91.4 ± 14.9; $P = 0.25$; Language, two-ventricle: 93.0 ± 18.4, single ventricle: 90.2 ± 17.7; $P = 0.44$).

All three Bayley-III scores demonstrated significant bivariate associations with patient race (Motor: $F_{2,108} = 6.0$, $P = 0.003$; Cognitive: $F_{2,108} = 5.8$, $P = 0.004$; Language: $F_{2,108} = 4.7$, $P = 0.011$), sex (Motor: $F_{1,109} = 22.1$, $P < 0.001$; Cognitive: $F_{1,109} = 9.2$, $P = 0.003$; Language: $F_{1,109} = 15.6$, $P < 0.001$), presence of genetic anomaly (Motor: $F_{2,108} = 11.9$, $P < 0.001$; Cognitive: $F_{2,108} = 5.0$, $P = 0.008$; Language: $F_{2,108} = 10.5$, $P < 0.001$), birth weight Z-score (Motor: $F_{1,109} = 9.4$, $P = 0.003$; Cognitive: $F_{1,109} = 7.5$, $P = 0.007$; Language: $F_{1,109} = 7.1$, $P = 0.009$), and exposure to extracorporeal membrane oxygenation (Motor: $F_{1,109} = 17.1$, $P < 0.001$; Cognitive: $F_{1,109} = 17.6$, $P < 0.001$; Language: $F_{1,109} = 11.2$, $P = 0.001$) (Supplemental Table 2). Bayley-III Cognitive and Language scores were associated with maternal education (Cognitive: $F_{3,107} = 5.0$, $P = 0.003$; Language: $F_{3,107} = 7.3$, $P < 0.001$), while Bayley-III Motor scores were not ($F_{3,107} = 2.1$, $P = 0.10$). These potentially confounding patient characteristics and logical confounders such as first admission length of stay were adjusted for as covariates in the final models for our primary confounders: exposures to sedation and anesthesia.

Table 5 displays the analysis of neurodevelopmental outcomes based on patients' exposures to sedation and anesthesia at first admission up to 18-month follow-up. All of the general linear model results presented in the table are individual regressions for each drug exposure separately. Adjusted for the variables listed in Table 5, no statistically significant associations were observed between cumulative volatile anesthetic agent exposure up to 18-month follow-up and Bayley-III Motor, Cognitive and Language scores. At 18-month follow-up, after adjusting for confounders, each mg/kg increase in ketamine use was associated with a 0.34-point decrease in Bayley-III Motor scores (Beta= −0.34; 95% CL= {−0.64, −0.05}; $P = 0.0242$). Even after removing the statistical outliers, the effect was statistically significant (Beta=−0.36; 95% CL= {−0.702, −0.0133), $P = 0.0419$). Exposures to opioids, benzodiazepines and dexmedetomidine were not associated with abnormal Bayley-III scores after adjusting for multiple covariates and statistical outliers (Table 5, Supplemental Table 3).

Discussion

The principal finding of this study is that total cumulative doses of volatile anesthetic agents at 18-month follow-up were not associated with neurodevelopmental impairment in infants who received general anesthesia and intensive care unit sedation for a variety of imaging studies and surgical and interventional cardiac procedures. However, cumulative ketamine exposure was associated with diminished motor scores. As previously demonstrated, non-modifiable patient factors such as race and presence of a genetic anomaly were associated with lower neurodevelopmental scores at 18-month follow-up.[12] We specifically focused this analysis on a patient population that experiences a substantial burden of cumulative anesthetic and sedative exposures early in life, as a meta-analysis of animal and human data suggested a dose dependency of deleterious outcomes.[23] In accordance with these findings, infants in this study were exposed to substantial cumulative anesthetic doses and considerable polypharmacy during perioperative and intensive care, with all receiving an inhaled anesthetic and a majority being exposed to opioids, ketamine, benzodiazepines, and barbiturates by 18 months of age. Due to the substantial disease burden in our patient cohort, these data cannot be compared with unexposed children, but rather must be assessed within the cohort by looking for a dose-response relationship.

This study differs from other studies that observed associations between cumulative exposures to sedative and anesthetic agents and worse neurodevelopmental outcomes in children after cardiac surgery. Andropoulos et al. reported an association between volatile anesthetic agent exposure during the first 12 months of life, brain injury, ICU length of stay, and lower Bayley-III Cognitive composite scores.[24] A similar study by Guerra et al. found no evidence of an association between dose and duration of sedation/analgesia drugs during the operative and perioperative period during the first 6 weeks of life and adverse neurodevelopmental outcomes.[25] Our study included a larger study population and a greater variety of sedative medications (e.g., ketamine, propofol, dexmedetomidine) in the multivariable analysis as well as a longer study duration of cumulative sedative and anesthetic medications for 18 months of life, which may help explain the discrepant results. Like our results, Andropoulos et al. also did not find any effect of cumulative volatile anesthetic dose on Bayley-III Motor or Language composite scores.

Diaz et al. reported in children with hypoplastic left heart syndrome and single ventricle variants, that greater cumulative duration of exposure to volatile anesthetic agents was associated with worse neurodevelopmental outcomes in certain domains at ages 4 and 5 years.[11] The contrasting results in our study may be attributed to the inclusion of patients with a broader range of congenital cardiac conditions; some patients might have been potentially less vulnerable to injury than the chronically cyanotic patients in the Diaz study. For example, we observed no association between Bayley-III Motor scores and volatile anesthetic agent exposures in the total cohort, yet the single-ventricle patients in our study had significantly lower scores when compared to two-ventricle patients. Our study also had less variability in exposures compared to the Diaz study, which may have contributed to the lack of an observed effect, and, in agreement with the current literature, identified maternal education as a confounder of neurodevelopmental outcome, which the Diaz study did not. Moreover, total MAC-h exposures over their 4- to 5-year study period were much

higher in the Diaz study than in our study, which primarily focused on exposures in infancy and assessed patients at 1.5 years of age. Patients undergoing staged reconstruction of single-ventricle physiology will have additional exposures, and in this small subset of single-ventricle patients, repeated anesthetic exposures and longer durations of anesthesia may exacerbate the risks of neurological injury.[11,26]

In our study, dexmedetomidine did not demonstrate a neuroprotective effect as seen in some animal studies when administered during volatile anesthetic agent exposures.[27,28] This might be explained by the comparatively lower perioperative dexmedetomidine doses in our clinical setting and the timing of the administration at our institution towards the end of the volatile anesthetic exposure. This agrees with our animal studies which also did not demonstrate any protective effects of dexmedetomidine administration during sevoflurane exposure.[28,29]

While cautioning against the use of ketamine, our findings suggest that in critically ill children undergoing major surgical procedures, such as repair of major congenital heart disease, factors other than volatile anesthetic exposure should be considered as potentially more impactful to alleviate postoperative neurodevelopmental impairment.[30] Indeed, the primary study found that greater concentrations of biomarkers of exposure to environmental chemicals, especially phthalates, were associated with poorer performance for language and motor skills at 18 months of age after adjustment for known risk factors for adverse neurodevelopment outcomes. Many of these chemicals are known endocrine-disrupting compounds and/or neurotoxicants, and we identified a greater adverse effect in girls compared to boys.[12] Periodic developmental surveillance, screening, and evaluation in children with congenital heart disease may enhance identification of significant deficits and enable appropriate education and therapy to improve neurodevelopment and functioning.[8] Novel intervention opportunities are being explored to improve neurodevelopmental outcomes in children with congenital heart disease during the perioperative period, through the utilization of new stratification schemata and cognitive interventions.[31,32] Research is also ongoing into elucidating the social determinants of health and outcomes for children with congenital heart disease; many of these factors are modifiable and are additional avenues to improve outcomes in these vulnerable patients.[33] Maternal anxiety in light of a diagnosis of congenital heart disease in their unborn child, for example, has also been demonstrated to adversely affect the baby's neurodevelopment and may be amenable to intervention.[34]

While Bayley Scales of Infant and Toddler Development are the most widely used standardized developmental test battery in medical and educational settings, a different neurodevelopmental assessment tool or testing at a later age might have resulted in alternative findings.[35] Evaluation at age 18 months may not predict later deficits, and the impact of anesthetic and sedative exposure may be greater on higher cognitive tasks such as executive function and social skills which can only be tested at an older age. A systematic review and meta-analysis of common prospectively collected outcomes showed that a single exposure to general anesthesia in early childhood was associated with statistically significant increases in parent reports of behavioral problems, but no difference in general intelligence.[36] However, that study used two different measures, a full-scale

intelligence quotient and parent-reported outcomes: Behavior Rating Inventory of Executive Function and Child Behavior Checklist. Another study reported that a correlation between learning disorders and anesthesia in children was of a lower magnitude than between learning disorders and hospitalization.[37] This heterogeneity in neurodevelopmental outcome measures is important to consider when assessing studies on the topic. Moreover, it is unclear whether the neonatal and infant periods represent the most susceptible period for potentially deleterious effects of anesthetic or sedative exposure in humans and how findings in immature animals can be translated into clinical practice.[38]

Our study has several additional limitations. First, any retrospective study is limited by confounders and cannot establish causation. While our analysis included many relevant covariates, other factors could certainly have influenced our observations. For example, in any study of neurologic outcomes in patients with congenital heart disease, it is important to determine whether there is an underlying syndromic diagnosis that in and of itself could impact outcomes. While all our patients underwent genetic assessment and major abnormalities were excluded, other undiagnosed genetic anomalies might have impacted our findings. Secondly, while our study was sufficiently powered to detect significant associations between neurodevelopmental scores and patient factors, it may have been underpowered to detect associations between anesthetic and sedative exposures and our outcomes of interest. A larger sample with the same exposure profile might have shown an effect. However, our results still support that patient factors were more impactful on neurocognitive outcomes than cumulative anesthetic or sedative exposures. Thirdly, due to an inability to measure volatile anesthetic agent concentrations in the cardiopulmonary bypass oxygenator, our analysis of volatile anesthetic agent exposure excluded volatile anesthetic agents administered during cardiopulmonary bypass, thereby underestimating total volatile anesthetic agent exposure in the study cohort and serving as a source of information bias. Fourthly, while we focused primarily on our analysis sans extreme outliers, these outliers highlight the importance of mindfulness when managing sedative use in infants with extremely long lengths of stay. Fifthly, since the potential neurological phenotype of anesthetic exposure remains unresolved, testing at an older age might differ from our assessment at 18 months and non-cognitive abnormalities were not assessed. Sixthly, 30 of 140 (21%) individuals were lost to follow-up, which is a potential source of selection bias. Seventhly, while we performed extensive manual review of the dataset, we did not use any formal methods to address missing data; data were assumed to be missing at random. Lastly, no standard pre- or perioperative assessment of baseline neurologic abnormalities was performed; these data were not collected as part of the primary study.[12]

Conclusion

In infants undergoing corrective and palliative surgery for major congenital heart disease, cumulative volatile anesthetic exposures were not associated with lower neurodevelopmental assessment scores at 18-month follow-up after adjusting for non-modifiable patient factors and length of stay. These findings contrast with studies that have shown volatile anesthetic exposure to be associated with worse neurodevelopmental outcomes in infants. However, greater ketamine exposure was associated with lower Bailey-III motor scores. Important differences between the substantial structural and functional abnormalities observed in

animals following prolonged anesthetic exposure and their clinical relevance for human infants require further research. Additional studies are needed to better understand timing of exposure relative to brain developmental state and to identify modifiable factors to improve neurodevelopmental outcomes in infants with congenital heart disease. Other factors beyond anesthetic neurotoxicity should be considered, such as additional perioperative factors and social determinants of health.[30]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Hailey Collier, PharmD, BCPPS, BCPS (Department of Pharmacy Services, Children's Hospital of Philadelphia, Philadelphia, PA, USA)

Funding Statement:

Supported by the Daniel M. Tabas and Alice Langdon Warner Endowed Chairs in Pediatric Cardiothoracic Surgery and NIH/NCATS (National Center for Advancing Translational Sciences): Grant UL1TR000003 and UL1TR001878.

References

1. Ing C, Warner DO, Sun LS, Flick RP, Davidson AJ, Vutskits L, McCann ME, O'Leary J, Bellinger DC, Rauh V, Orser BA, Suresh S, Andropoulos DB. Anesthesia and developing brains: Unanswered questions and proposed paths forward. Anesthesiology. 2022; 136:500–512. [PubMed: 35015802]
2. McCann ME, Soriano SG. Does general anesthesia affect neurodevelopment in infants and children?. BMJ. 2019; 367:l6459. [PubMed: 31818811]
3. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. Nat Rev Neurosci. 2016; 17:705–717. [PubMed: 27752068]
4. Jevtovic-Todorovic V. Exposure of developing brain to general anesthesia: what is the animal evidence?. Anesthesiology. 2018; 128:832–839. [PubMed: 29271804]
5. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, Hardy P, Hunt RW, Takagi MJ, Giribaldi G, Hartmann PL, Salvo I, Morton NS, von Ungern Sternberg BS, Locatelli BG, Wilton N, Lynn A, Thomas JJ, Polaner D, Bagshaw O, Szmuk P, Absalom AR, Frawley G, Berde C, Ormond GD, Marmor J, McCann ME; GAS consortium. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial [published correction appears in Lancet. 2016;387(10015):228]. Lancet. 2016;387(10015):239–250. [PubMed: 26507180]
6. McCann ME, de Graaff JC, Dorris L, Disma N, Withington D, Bell G, Grobler A, Stargatt R, Hunt RW, Sheppard SJ, Marmor J, Giribaldi G, Bellinger DC, Hartmann PL, Hardy P, Frawley G, Izzo F, von Ungern Sternberg BS, Lynn A, Wilton N, Mueller M, Polaner DM, Absalom AR, Szmuk P, Morton N, Berde C, Soriano S, Davidson AJ; GAS Consortium. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial [published correction appears in Lancet. 2019;394(10199):638]. Lancet. 2019;393(10172):664–677. [PubMed: 30782342]
7. Sun LS, Li G, Miller TL, Salorio C, Byrne MW, Bellinger DC, Ing C, Park R, Radcliffe J, Hays SR, DiMaggio CJ, Cooper TJ, Rauh V, Maxwell LG, Youn A, McGowan FX. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA. 2016; 315:2312–2320. [PubMed: 27272582]

8. Snookes SH, Gunn JK, Eldridge BJ, Donath SM, Hunt RW, Galea MP, Shekerdemian L. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. Pediatrics. 2010; 125:e818–27. [PubMed: 20231182]

9. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, Beca J, Donofrio MT, Duncan K, Ghanayem NS, Goldberg CS, Hövels-Gürich H, Ichida F, Jacobs JP, Justo R, Latal B, Li JS, Mahle WT, McQuillen PS, Menon SC, Pemberton VL, Pike NA, Pizarro C, Shekerdemian LS, Synnes A, Williams I, Bellinger DC, Newburger JW; International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics. 2015; 135:816–25. [PubMed: 25917996]

10. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012; 126:1143–72. [PubMed: 22851541]

11. Diaz LK, Gaynor JW, Koh SJ, Ittenbach RF, Gerdes M, Bernbaum JC, Zackai EH, Clancy RR, Rehman MA, Pennington JW, Burnham N, Spray TL, Nicolson SC. Increasing cumulative exposure to volatile anesthetic agents is associated with poorer neurodevelopmental outcomes in children with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg. 2016; 152:482–9. [PubMed: 27183886]

12. Gaynor JW, Burnham NB, Ittenbach RF, Gerdes M, Bernbaum JC, Zackai E, Licht DJ, Russell WW, Zullo EE, Miller T, Hakonarson H, Clarke KA, Jarvik GP, Calafat AM, Bradman A, Bellinger DC, Henretig FM, Coker ES. Childhood exposures to environmental chemicals and neurodevelopmental outcomes in congenital heart disease. PLoS One. 2022;17:e0277611. [PubMed: 36395323]

13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007; 335:806–8 [PubMed: 17947786]

14. Hollingshead A. Four Factor Index of Social Status. New Haven, CT: Yale University; 1975.

15. Clancy RR, McGaurn SA, Wernovsky G, Spray TL, Norwood WI, Jacobs ML, Murphy JD, Gaynor JW, Goin JE. Preoperative risk-of-death prediction model in heart surgery with deep hypothermic circulatory arrest in the neonate. J Thorac Cardiovasc Surg. 2000; 119:347–57. [PubMed: 10649211]

16. Bayley N. Bayley scales of infant and toddler development. San Antonio, Texas: Pearson Education, Inc; 2006.

17. Cameron CB, Robinson S, Gregory GA. The minimum anesthetic concentration of isoflurane in children. Anesth Analg. 1984; 63:418–20. [PubMed: 6703367]

18. Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. Anesthesiology. 1994; 80:814–24. [PubMed: 8024136]

19. Taylor RH, Lerman J. Minimum alveolar concentration of desflurane and hemodynamic responses in neonates, infants, and children. Anesthesiology. 1991;75: 975–9. [PubMed: 1741518]

20. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. N Engl J Med. 2003; 348:959–60. [PubMed: 12621144]

21. Warrington SE, Collier HK, Himebauch AS, Wolfe HA. Evaluation of IV to enteral benzodiazepine conversion calculations in a pediatric intensive care setting. Pediatr Crit Care Med. 2018; 19:e569–e75. [PubMed: 30080777]

22. SAS Institute Inc. 2013. Base SAS® 9.4 Procedures Guide: Statistical Procedures, Second Edition. Cary, NC: SAS Institute Inc.

23. Lin EP, Lee JR, Lee CS, Deng M, Loepke AW. Do anesthetics harm the developing human brain? An integrative analysis of animal and human studies. Neurotoxicol Teratol 2017; 60:117–128. [PubMed: 27793659]

24. Andropoulos DB, Ahmad HB, Haq T, Brady K, Stayer SA, Meador MR, Hunter JV, Rivera C, Voigt RG, Turcich M, He CQ, Shekerdemian LS, Dickerson HA, Fraser CD, Dean

McKenzie E, Heinle JS, Blaine Easley R. The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study. Pediatr Anaesth 2014; 24:266–74

25. Guerra GG, Robertson CM, Alton GY, Joffe AR, Cave DA, Dinu IA, Creighton DE, Ross DB, Rebeyka IM; Western Canadian Complex Pediatric Therapies Follow-up Group. Neurodevelopmental outcome following exposure to sedative and analgesic drugs for complex cardiac surgery in infancy. Pediatr Anesth 2011; 21: 932–941.
26. Warner DO, Zaccariello MJ, Katusic SK, Schroeder DR, Hanson AC, Schulte PJ, Buenvenida SL, Gleich SJ, Wilder RT, Sprung J, Hu D, Voigt RG, Paule MG, Chelonis JJ, Flick RP. Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: the Mayo Anesthesia Safety in Kids (MASK) study. Anesthesiology. 2018;129:89–105. [PubMed: 29672337]
27. Sanders RD, Xu J, Shu Y, Januszewski A, Halder S, Fidalgo A, Sun P, Hossain M, Ma D, Maze M. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology. 2009;110:1077–1085. [PubMed: 19352168]
28. Lee JR, Joseph B, Hofacer RD, Upton B, Lee SY, Ewing L, Zhang B, Danzer SC, Loepke AW. Effect of dexmedetomidine on sevoflurane-induced neurodegeneration in neonatal rats. Br J Anaesth. 2021;126:1009–1021. [PubMed: 33722372]
29. Lee JR, Lin EP, Hofacer RD, Upton B, Lee SY, Ewing L, Joseph B, Loepke AW. Alternative technique or mitigating strategy for sevoflurane-induced neurodegeneration: a randomized controlled dose-escalation study of dexmedetomidine in neonatal rats. Br J Anaesth. 2017;119:492–505. [PubMed: 28969315]
30. McCann ME, Lee JK, Inder T. Beyond anesthesia toxicity: anesthetic considerations to lessen the risk of neonatal neurological injury. Anesth Analg. 2019; 129:1354–64. [PubMed: 31517675]
31. Marino BS. New concepts in predicting, evaluating, and managing neurodevelopmental outcomes in children with congenital heart disease. Curr Opin Pediatr. 2013;25:574–84. [PubMed: 23995435]
32. Calderon J, Bellinger DC, Hartigan C, Lord A, Stopp C, Wypij D, Newburger JW. Improving neurodevelopmental outcomes in children with congenital heart disease: protocol for a randomised controlled trial of working memory training. BMJ Open. 2019;9:e023304.
33. Davey B, Sinha R, Lee JH, Gauthier M, Flores G. Social determinants of health and outcomes for children and adults with congenital heart disease: a systematic review. Pediatr Res. 2021;89:275–294. [PubMed: 33069160]
34. De Asis-Cruz J, Krishnamurthy D, Zhao L, Kapse K, Vezina G, Andescavage N, Quistorff J, Lopez C, Limperopoulos C. Association of prenatal maternal anxiety with fetal regional brain connectivity. JAMA Netw Open. 2020; 3:e2022349. [PubMed: 33284334]
35. Backeljauw B, Holland SK, Altaye M, Loepke AW. Cognition and brain structure following early childhood surgery with anesthesia. Pediatrics. 2015;136:e1–12. [PubMed: 26055844]
36. Ing C, Jackson WM, Zaccariello MJ, Goldberg TE, McCann ME, Grobler A, Davidson A, Sun L, Li G, Warner DO. Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis. Br J Anaesth. 2021;126:433–444. [PubMed: 33250180]
37. Laudenbach V, Charollais A, Radi S, Stumpf MH, Vincent A, Kaltwasser I, Tomczyk T, Benichou J, Leroux P, Marret S. Conditions requiring hospitalisations, more than general anaesthesia itself, are associated with diagnosis of learning disorders in children. Anaesth Crit Care Pain Med. 2020; 39:777–783. [PubMed: 32977071]
38. Mintz CD, Wagner M, Loepke AW. Preclinical research into the effects of anesthetics on the developing brain: promises and pitfalls. J Neurosurg Anesthesiol. 2012; 24:362–7. [PubMed: 23076224]

Table 1.

Demographic and clinical data of the study cohort, n = 110 and live patients lost to follow-up (live non-returners), n = 20.[12]

	Study Cohort		Live Non-Returners, n = 20	
	Frequency (%)	**Median (IQR)**	**Frequency (%)**	**Median (IQR)**
Patient characteristics				
Gestational age, weeks		39.1 (38.4, 39.6)		39.1 (37.6, 39.3)
Birth weight, kg		3.3 (3.0, 3.6)		3.2 (2.8, 3.5)
Birth weight, Z-score		0.0 (−0.7, 0.6)		−0.1 (−1.1, 0.5)
Birth head circumference, Z-score		−0.3 (−1.2, 0.8)		−0.7 (−1.6, 0.1)
Age at first surgery, days		5 (3, 6)		4 (3, 11)
First admission length of stay, days		15 (11, 23)		14 (10, 21)
Total inpatient days at age 18 months		19 (12, 41)		
Sex				
Male	68 (62%)		11 (55%)	
Female	42 (38%)		9 (45%)	
Race				
White	89 (81%)		12 (60%)	
African American	6 (6%)		3 (15%)	
Other	15 (13%)		5 (25%)	
Genetic Anomaly				
None	78 (71%)		16 (80%)	
Suspected	14 (13%)		4 (20%)	
Abnormal	18 (16%)		0	
Noncardiac Genetic Anomaly				
None	78 (73%)			
1 or more	32 (27%)			
Cardiac Diagnosis Class				
I: 2 ventricles/no arch obstruction	53 (48%)		11 (55%)	
II: 2 ventricles/arch obstruction	16 (15%)		3 (15%)	
III: 1 ventricle/no arch obstruction	9 (8%)		1 (5%)	
IV: 1 ventricle/arch obstruction	32 (29%)		4 (25%)	
Highest Maternal Education				
Junior high school (7th, 8th, & 9th grades)	1 (1%)			
Partial high school (10th & 11th grades)	5 (5%)		1 (6%)	
Graduated high school (12th grade)	10 (9%)		2 (13%)	
Partial college or trade school	16 (15%)		3 (19%)	
College graduate	50 (46%)		4 (25%)	
Post graduate degree	28 (26%)		6 (38%)	
Anesthetic, Surgical, and Hospital Data				
Extracorporeal membrane oxygenation	3 (3%)		1 (5%)	
Additional Surgical Procedures with Cardiopulmonary Bypass				

	Study Cohort		Live Non-Returners, n = 20	
	Frequency (%)	**Median (IQR)**	**Frequency (%)**	**Median (IQR)**
None	66 (60%)		12 (60%)	
1 or more	44 (40%)		8 (40%)	

Abbreviation – IQR, interquartile range

Table 2.

Counts and percentages of patients exposed to each medication up to 18-month follow up, by cardiac diagnosis class and total subject cohort

Medication	Class I (n =53)	Class II (n =16)	Class III (n =9)	Class IV (n =32)	All subjects (n=110)
Fentanyl	53 (100%)	15 (94%)	9 (100%)	32 (100%)	109 (99%)
Ketamine	46 (87%)	15 (94%)	9 (100%)	31 (97%)	101 (92%)
Morphine	43 (81%)	13 (81%)	9 (100%)	32 (100%)	97 (88%)
Oxycodone	39 (74%)	5 (31%)	6 (67%)	30 (94%)	80 (73%)
Pentobarbital	26 (49%)	4 (25%)	6 (67%)	31 (97%)	67 (61%)
Midazolam	24 (45%)	6 (38%)	6 (67%)	31 (97%)	67 (61%)
Dexmedetomidine	11 (21%)	7 (44%)	8 (89%)	32 (100%)	58 (53%)
Diazepam	3 (6%)	1 (6%)	1 (11%)	6 (19%)	11 (10%)
Phenobarbital	0 (0%)	1 (6%)	0 (0.0%)	6 (19%)	7 (6%)
Propofol	6 (11%)	6 (38%)	3 (33%)	11 (34%)	26 (24%)
Lorazepam	1 (2%)	1 (6%)	0 (0.0%)	2 (6%)	4 (4%)
Meperidine	4 (8%)	1 (6%)	2 (22%)	2 (6%)	9 (8%)
Remifentanil	0 (0%)	1 (6%)	0 (0%)	0 (0%)	1 (1%)
Hydromorphone	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Cardiac Diagnosis Classes: I: 2 ventricles/no arch obstruction, II: 2 ventricles/arch obstruction, III: 1 ventricle/no arch obstruction, IV: 1 ventricle/arch obstruction

Table 3.

Summary of weight-adjusted anesthetic and sedative exposures at 18-month follow up in the study cohort (n=110)

Anesthetic or Sedative Exposure	Units	Mean	Std Dev	Minimum	5th %ile	25th %ile	Median	75th %ile	95th %ile	Maximum
Volatile anesthetic agents	MAC-hr	2.4	2.5	0.0	0.1	0.6	1.6	3.4	8.2	15.0
Dexmedetomidine, perioperative	mcg/kg	1.1	1.5	0.0	0.0	0.0	0.0	2.0	4.1	6.3
Opioids, perioperative and ICU	mg/kg, MOEQ	15.5	49.1	0.2	0.8	1.5	3.5	10.3	42.0	403.3
Benzodiazepines, perioperative and ICU	mg/kg	6.6	39.1	0.0	0.0	0.0	0.1	0.5	6.1	341.9
Dexmedetomidine, perioperative and ICU	mcg/kg	8.0	12.5	0.0	0.0	0.0	1.0	12.7	35.6	65.6
Ketamine, perioperative and ICU	mg/kg	7.4	7.2	0.0	0.0	2.0	5.4	10.4	21.5	45.6

Note: Opioids and benzodiazepines were converted to weight-adjusted intravenous morphine and midazolam equivalent doses, respectively. Volatile anesthetic agents include sevoflurane, desflurane, and isoflurane.

Abbreviations: ICU - intensive care unit; MAC - minimum alveolar concentration; MOEQ - morphine equivalent; Std Dev - standard deviation; %ile - percentile

Table 4.

Bayley Scales of Infant and Toddler Development, Third Edition, Motor, Cognitive, and Language scores of entire study cohort and grouped by cardiac diagnosis class

Study Cohort Group	Bayley-III Scale	Mean	Std Dev	Minimum	25th Percentile	Median	75th Percentile	Maximum
All patients	Motor	92.0	11.7	52	85	94	100	118
(n = 110)	Cognitive	93.2	12.7	53	90	95	100	125
	Language	92.0	18.1	47	79	91	106	132
Cardiac Class I or II	Motor	94.4	9.3	67	89	97	108	112
(n = 69)	Cognitive	94.3	11.1	55	90	95	100	125
	Language	93.0	18.4	47	79	91	106	132
Cardiac Class III or IV	Motor	87.8	14.0	52	67	88	109	118
(n = 41)	Cognitive	91.4	14.9	53	85	95	100	120
	Language	90.2	17.7	55	77	91	106	124

Abbreviations: Std Dev - standard deviation

Cardiac Diagnosis Classes: I: 2 ventricles/no arch obstruction, II: 2 ventricles/arch obstruction, III: 1 ventricle/no arch obstruction, IV: 1 ventricle/arch obstruction

Table 5.

Unadjusted and adjusted general linear model analyses of Bayley Scales of Infant and Toddler Development, Third Edition scores and cumulative exposures to sedation and anesthesia at 18-month follow-up visit (n=110)

Anesthetic or Sedative Exposure	Bayley III: Motor Score			Bayley III: Cognitive Score			Bayley III: Language Score		
	Beta Coefficient 95% CL			Beta Coefficient 95% CL			Beta Coefficient 95% CL		
	Unadjusted (bivariate)^	Adjusted for VAA exposure^^	Adjusted for multiple covariates^^^	Unadjusted (bivariate)^	Adjusted for VAA exposure^^	Adjusted for multiple covariates^^^	Unadjusted (bivariate)^	Adjusted for VAA exposure^^	Adjusted for multiple covariates^^^
Volatile anesthetic agents, MAC-hours	−1.62**	--	−0.54	−1.33**	--	−0.20	−1.08	--	0.22
	(−2.46, −0.77)		(−1.41, 0.32)	(−2.30, −0.38)		(−1.24, 0.84)	(−2.46, 0.30)		(−1.18, 1.61)
Opioids, perioperative and ICU, mg/kg, MOEQ	−0.09	−0.07**	0.06	−0.09**	−0.07**	0.02	−0.10**	−0.10*	0.005
	(−0.13, −0.05)	(−0.12, −0.02)	(−0.03, 0.15)	(−0.13, −0.04)	(−0.13, −0.02)	(−0.08, 0.13)	(−0.17, −0.03)	(−0.18, −0.02)	(−0.14, 0.15)
Benzodiazepines, perioperative and ICU, mg/kg	−0.10**	−0.07*	−0.02	−0.07*	−0.04	0.01	−0.11*	−0.09	−0.02
	(−0.16, −0.05)	(−0.13, −0.01)	(−0.08, 0.04)	(−0.13, −0.01)	(−0.10, 0.03)	(−0.06, 0.08)	(−0.19, −0.02)	(−0.19, 0.004)	(−0.11, 0.07)
Dexmedetomidine, perioperative and ICU, mcg/kg	−0.24**	−0.04	−0.17	−0.18*	0.03	−0.15	−0.16	−0.04	−0.27
	(−.41,−0.06)	(−2.60, −0.34)	(−1.04, 1.15)	(−0.38,0.001)	(−2.50, 0.03)	(−0.37, 0.08)	(−0.44, 0.11)	(−2.80, 0.89)	(−0.57, 0.03)
Ketamine, perioperative and ICU, mg/kg	−0.51**	−0.31	−0.34*	−0.26	−0.05	−0.18	−0.15	−0.05	−0.07
	(−0.80, −0.22)	(−2.13, −0.19)	(−0.64, −0.05)	(−0.59, 0.07)	(−2.36, −0.16)	(−0.54, 0.19)	(−0.63, 0.32)	(−2.76, 0.46)	(−0.56, 0.42)

* P-value < 0.05;

** P-value < 0.01

Note: These are all individual regressions for each drug.

^ The unadjusted general linear model analyses are bivariate models with the outcome regressed on each individual drug exposure separately with no covariates.

^^ The adjusted general linear analyses model included the following variables: each individual exposure separately and the volatile anesthetic agent exposure up to the 18-month follow-up.

^^^ The adjusted general linear model analyses included the following variables: each individual drug exposure separately, the single volatile anesthetic agent exposure up to the 18-month follow-up, presence of a genetic anomaly, patient sex, patient race, patient mother's highest education level, cardiac diagnosis class, extracorporeal membrane oxygenation requirement in the intensive care unit, patient birth weight Z-score, and first hospitalization length of stay.

Abbreviations: ICU, intensive care unit; VAA, volatile anesthetic agents (sevoflurane, desflurane, isoflurane); SE, standard error; CL, confidence limits; MAC, minimum alveolar concentration; MOEQ, morphine equivalents