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Duration of Exposure to Cranial Vault Surgery: Associations with Neurodevelopment among Children with Single-Suture Craniosynostosis

Heather L. Naumann, M.D.^{1,2} [Acting Assistant Professor], Charles M. Haberkern, M.D., M.P.H.^{1,2,3} [Professor, Adjunct Professor], Kristen E. Pietila, M.S.⁴, Craig B. Birgfeld, M.D.^{2,5} [Assistant Professor], Jacqueline R. Starr, Ph.D.^{6,4} [Associate Research Investigator, Affiliate Associate Professor], Kathleen A Kapp-Simon, Ph.D.^{7,8} [Associate Professor], Richard A. Hopper, M.D.^{2,5} [Associate Professor], and Matthew L. Speltz, Ph.D.^{2,9} [Professor]

¹Department of Anesthesiology & Pain Medicine, University of Washington, Seattle

²Seattle Children's Hospital, Seattle

³Department of Pediatrics, University of Washington, Seattle

⁴Department of Epidemiology, University of Washington, Seattle

⁵Department of Surgery, University of Washington, Seattle

⁶The Forsyth Institute, Cambridge, MA

⁷Department of Surgery, Northwestern University, Chicago

⁸Shriners Hospital for Children, Chicago

⁹Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle

Abstract

Objective—To evaluate associations between neurodevelopment and exposure to surgery and anesthetic agents in children with single-suture craniosynostosis (SSC).

Background—Young children with SSC have unexplained neurodevelopmental delays. The possible contributions of factors related to cranial vault surgery—including anesthesia—have not been previously examined.

Methods/Materials—Two anesthesiologists reviewed the surgical records of 89 infants (70 had complete data). Primary exposures were duration of surgery and anesthesia and total duration of inhaled anesthesia (at age 6 months on average). Outcomes were the cognitive and motor scores from the Bayley Scales of Infant Development-II and language scores from the Preschool Language Scale, 3rd edition, given at age 36 months. Linear regression using robust standard error estimates was performed, adjusting for age at surgery and suture site.

Results—Anesthesia duration ranged from 155 to 547 minutes. For every 30-minute increase in anesthesia duration, the estimated average decrease in developmental test scores ranged from 1.1 to 2.9 (p ranged from <0.001 to 0.30). Similar, but weaker findings were observed with surgery duration and total duration of inhaled anesthesia. Inverse relations between exposure amounts and neurodevelopment were stronger in children with non-sagittal synostosis.

Conclusions—Average neurodevelopmental scores were lower among children experiencing longer surgeries and higher exposures to inhaled anesthesia. These associations may be due to anesthesia exposure, nonspecific effects of surgery, or unmeasured variables that correlate with surgery duration. Further study of potential causal mechanisms is warranted.

INTRODUCTION

Single-suture craniosynostosis (SSC) is the premature fusion of one suture in an infant's skull, which occurs in approximately 1 in 2000 live births. Infants with SSC usually undergo cranial vault surgery in the first year of life in order to minimize secondary facial deformation and the potential effects of intracranial pressure (ICP).⁽¹⁾ In prospective research, infants and young children with SSC have shown cognitive and motor delays in relation to demographically matched control group children,^(2,3) and studies of clinical samples have suggested a continuing risk of learning and language disabilities during childhood and adolescence.⁽⁴⁾ The causes of these delays are yet unknown but believed to reflect multiple factors.⁽⁵⁾

One as yet unexplored possibility is that some aspect of surgery influences neurocognitive outcomes, since most children with SSC undergo lengthy surgical procedures while few, if any, control group children experience comparable exposure to surgical interventions. To our knowledge there has been no previous study of associations between neurodevelopment and the procedural details of cranial vault surgery, such as duration of surgery and anesthesia, type of anesthesia, amount of blood loss and occurrence of adverse events. Many of these factors, including anesthesia, could adversely affect development of the infant brain.^(6,7)

As a starting point in the study of this issue, we examined the dose-response relationship between (a) duration of cranial vault surgery, total duration of anesthesia, and total amount of inhaled anesthesia at an average age of 6 months and (b) infants' neurodevelopmental status at age 36 months. We evaluated the hypothesis that after accounting for confounding factors (e.g., suture diagnosis, age of surgery), duration of surgery and anesthesia and amounts of inhaled anesthesia would be inversely related to neurodevelopmental outcomes.

MATERIALS AND METHODS

Participants

Participants were infants with SSC recruited from Seattle Children's Hospital (SCH). The SCH participants were part of a larger multicenter follow-up study.⁽²⁾ Participants were enrolled after obtaining informed consent approved by the Institutional Review Board at SCH in full compliance with HIPAA standards. Infants 30 months of age or younger were eligible if they: (1) had SSC confirmed by computed tomography (sagittal, metopic,

unilateral coronal synostosis, or unilateral lambdoid synostosis); (2) had no identifiable syndrome associated with SSC; and (3) were scheduled for reconstructive surgery at SCH (for exclusion criteria see (2)).

We identified 123 eligible participants during the recruiting period and 96 were enrolled (10 families actively and 17 passively declined participation). Among the 96 enrolled patients, 7 had surgery at institutions other than SCH (and were therefore ineligible for this study), 18 were lost to follow-up, and one participant had invalid outcome data. This left a total of 70 participants with complete surgical records and one or more neurodevelopmental outcome measures (57% of the 123 originally eligible).

Measures

Two anesthesiologists (CH and HN) reviewed the anesthetic paper records and documents relating to both the intraoperative period (the time between induction of anesthesia and admission to intensive care unit, ICU) and the postoperative period (time between admission to and discharge from ICU). We recorded the following: duration of anesthesia and surgery (minutes); exposure to all anesthetic and analgesic agents; blood product replacement (milliliters, ml) in the perioperative period (i.e., intra- and postoperative periods); and intraoperative oxygen exposure. We also recorded the occurrence of any adverse perioperative events (see Table 4).

For all intravenous agents, total perioperative exposure was measured in micrograms per kilogram body weight (mcg/kg) or milligrams per kilogram (mg/kg), as appropriate to each agent. Due to the small number of participants receiving either lorazepam or midazolam, these variables were dichotomized as yes/no. Propofol was measured in mg/kg, and intra- and postoperative morphine was measured in mcg/kg; total doses of propofol were divided by 10 to reflect 10-unit increases in the analysis, whereas total morphine dose was divided by 100. For volatile anesthetic agents, each fifteen-minute interval of exposure was quantified by minutes multiplied by the age-corrected Mean Alveolar Concentration (MAC) equivalent for the particular agent (measured in 0.5 MAC units) (8,9). Exposures 15 minutes during induction only were not included in the analyses. From medical records and/or directed parental interviews, we recorded the number of additional anesthetic exposures that occurred before or after initial cranial vault surgery and before the 36-month assessment.

All covariates measured by duration of exposure (surgical time, anesthesia duration, total inhaled anesthetic exposure, exposure to sevoflurane and isoflurane individually) were expressed in 30-minute increments (i.e., dividing total time by 30). Red blood cells (RBCs) and fresh frozen plasma (FFP) were measured in ml/kg and were grouped into 10 ml/kg units by dividing totals by 10.

Bayley Scales of Infant Development, Second Edition (BSID-II)—The well-validated BSID-II was used to measure infants' cognitive and psychomotor status.(10) Performance was summarized by the Mental Development Index (MDI) and Psychomotor Development Index (PDI). Like an IQ score, both indices have an average score of 100 in the population (standard deviation = 15).

Language Functioning—The Preschool Language Scale, Third Edition (PLS) was used to assess expressive and receptive language skills.(11) The PLS is a norm-referenced test of infant language that yields two summary scores: receptive (PLS-AC) and expressive (PLS-EC) language.

Examiner training and reliability—All BSID-II and PLS-3 assessments were performed by trained psychometrists whose test administrations were reviewed for accuracy by one of the investigators (KK-S) prior to the study. Approximately 10% of all subjects had a video review of one of their assessments, which was independently scored by KK-S, who calculated exact agreement with the tester on individual test items. The resulting inter-observer agreements were 96.5% for items comprising the MDI, 93% for PDI items, and 98.9% for both the PLS-AC and PLS-EC items.

Statistical Analysis

To estimate associations between neurodevelopment and surgery-related exposures, we performed linear regression analyses with 95% confidence intervals based on robust standard error estimates.

Outcome and exposure variables—The standardized scores for each of the four measures of neurodevelopmental status (MDI, PDI, PLS-AC and PLS-EC) served as outcome variables in separate regression models. The primary exposures were those we hypothesized to have the strongest effects: (1) duration of anesthesia exposure; (2) duration of surgery; and (3) total exposure to inhaled anesthetic. Eight secondary exposure variables related to specific anesthetic/analgesic agents or blood loss were examined in exploratory analyses, including (1) sevoflurane; (2) isoflurane; (3) lorazepam; (4) midazolam; (5) propofol; and (6) morphine (morphine administration was used as a proxy for opioid exposure since all patients received morphine and potencies for other opioids variably administered differ); (7) total units of RBCs and (8) FFP.

Confounders—Given the number of covariates in relation to sample size, we used a strategy in which we identified *a priori* the most likely potential confounders (age at surgery as a continuous variable, and site of the affected suture: sagittal, metopic, coronal, or lambdoid), as well as other covariates that could be confounders but less likely to be so. We included the first two in all regression models. Surgery age was selected because of its correlation with severity of craniosynostosis (older cases may have milder phenotypes) and bone thickness, which may affect the complexity and length of surgery. Suture site was selected because it is related to surgical method and duration of surgery, as well as the occurrence of certain adverse events (e.g., venous air embolisms(12)).

We subsequently explored potential confounding by the additional covariates.(13) This process involved six sensitivity analyses in which we refit regression models to assess whether estimates meaningfully changed after separately adjusting for either: (1) gender; (2) race; (3) neurodevelopmental scores at baseline (e.g., pre-surgical MDI when outcome was MDI); (4) intra- or postoperative hematocrit < 25% and (5) perioperative coagulopathy (all

other recorded adverse events either did not occur or were too infrequent for analysis); or (6) total amount of RBCs (ml/kg) administered intra- and postoperatively.

Effect modification of additional procedures—We refit the regressions to include an interaction term for the number of additional procedures involving anesthesia (1 versus 0) before follow-up. We performed Wald tests for the interaction terms and examined the stratified estimates for differences.

Differences by diagnostic group—The average length of surgery for children diagnosed with sagittal synostosis was shorter than that for children with premature fusion of the metopic, coronal, or lambdoid sutures. We therefore examined the exposure-outcome associations separately for the two diagnostic subgroups: sagittal and non-sagittal synostosis.

Exploration of the dose-response curve—To evaluate the dose-response curve without imposing a linear relationship (as in the analyses above), we also grouped subjects into quartiles of exposure and refit regression models including indicator variables for the 2nd, 3rd, and 4th quartiles compared with the 1st or “least exposed” quartile (i.e. shortest surgery or anesthesia durations or fewest MAC minutes of anesthesia dose). These models were adjusted for age at surgery and affected suture.

All analyses were performed using STATA version 10.0 (Stata Corp., College Station, Texas).(14) Given the exploratory nature of this research, we did not adjust *p*-values for multiple comparisons, nor did we interpret *p*-values as dichotomous significance tests. Rather, we evaluated the magnitude of observed associations and the precision of such estimates based on confidence intervals.(15,16)

RESULTS

The majority of subjects were male, white, and of higher socioeconomic status (Table 1). Approximately half had sagittal synostosis; close to half underwent frontal-orbital advancement, and a similar proportion posterior vault modified pi procedures (Table 1).

All patients were exposed to volatile anesthetic agents as part of maintenance anesthesia, in most cases either isoflurane (70.0%) or sevoflurane (38.6%); six patients received both. In addition, all patients received intra- or postoperative opioids (morphine, fentanyl and/or remifentanyl) and 57.1% received propofol as part of their anesthetic regimen (Table 2).

Mean neurodevelopmental scores were in the average to low average range both before and after surgery (Table 3). The frequencies of all recorded perioperative events are shown in Table 4.

Primary exposures

The three primary exposures each had negative associations with all four measures of neurodevelopment (Table 5). For every 30-minute increase in anesthesia duration, the estimated decrease in the four developmental outcome scores ranged from 1.1 to 2.9 (*p* ranged from <0.001 to 0.30). For total surgical time and total exposure to inhaled anesthetic

agents, associations were generally weaker than for total duration of anesthesia: for every 30-minute increase in surgery duration, the estimated decrease in outcome scores ranged from 0.2 to 2.8 (p ranged from 0.003 to 0.85). The estimated decrease in outcome scores for every 30-MAC minute increase in inhaled anesthesia ranged from 0.9 to 1.8 (p ranging from 0.02 to 0.17).

Confounders

None of the six potential confounders, including presurgery neurodevelopmental scores and total RBCs administered, meaningfully altered the estimates for any of the primary exposures.

Secondary exposures

Associations between outcomes and the eight secondary exposure variables were similar to those observed between outcomes and the primary exposures. Most associations were negative, although generally weaker and having wider confidence intervals than associations involving the primary exposures (see Supplementary Table 1). Regarding the two commonly-used inhaled anesthetic agents, isoflurane showed consistently negative associations with outcomes (estimated decreases in outcome scores ranged from 1.5 to 2.5; p ranged from 0.007 to 0.13), while sevoflurane showed mostly negative, but very weak associations with outcomes (estimated change in scores ranged from -0.4 to 0.0; p ranged from 0.62 to 0.98). No other single agent was notably more or less predictive of outcome scores than any other agent.

Effect modification of additional anesthesia exposures

No interactions were observed between the primary exposures and the number of additional anesthesia exposures.

Diagnostic group differences

Associations between the primary exposures and outcomes tended to be stronger among patients with non-sagittal synostosis (Table 6). In analyses restricted to subjects with sagittal synostosis, associations were less consistently negative and tended to be closer to the null than analogous associations measured in the overall group.

Exploration of the dose-response curve

The exposure group for which we observed consistently negative associations with neurodevelopmental outcomes was the fourth quartile—those with the longest surgery and anesthesia durations compared to the shortest, and greatest amount of inhaled anesthetic exposure versus the lowest (e.g., for anesthesia duration, the average decrease in test scores ranged from 22 to 5 points when comparing the fourth to first quartile exposure groups across outcome measures).

DISCUSSION

Among infants with SSC we observed inverse associations between neurodevelopment and duration of cranial vault surgery. With increasing duration of surgery and associated

exposure to anesthesia at ~ 6 months of age, we found lower cognitive, motor and language scores at 36 months of age. When considering only duration of anesthesia, cognitive scores were on average approximately 2.5 points lower for every 30-minute increase in exposure. Across the range of anesthesia durations in this sample (e.g., 155 to 547 minutes), relatively large and clinically meaningful decrements in neurodevelopment were therefore apparent. For example, based on the average dose-response relationship, infants experiencing the longest exposure to anesthesia (i.e., the 4th quartile, > 7.4 hours of exposure) had MDI scores (mental development) approximately 16 points (or 1 standard deviation) lower than those experiencing the briefest exposure (i.e., 1st quartile, < 4.2 hours of exposure). Such differences were more pronounced for PDI scores (psychomotor development). For surgery duration, these relationships were similar but not nearly as strong. For example, the 4th quartile of surgery durations had MDI scores approximately 4.2 points lower than those in the first quartile.

We reanalyzed these associations by affected suture (sagittal or non-sagittal) and found them to be stronger in children with non-sagittal synostosis (i.e., metopic, unicoronal and lambdoid combined). Because surgery durations were longer for subjects with non-sagittal synostosis, this pattern suggests a possible threshold dose-response effect, whereby only children who surpass a particular exposure level are affected. This effect has been observed among infants undergoing hypothermic circulatory arrest during heart surgery.(17)

The inverse relations between exposure doses and neurodevelopment could be due to any one or more of several factors. Although the design of this study precludes reliable examination of casual pathways, it is useful at this stage of investigation to consider possible explanatory mechanisms. Previous research has suggested that anesthesia exposure very early in life may lead to neurotoxicity in human infants,(18-21) although other studies have found little evidence for such effects.(22-24) There may also be nonspecific effects from the surgery itself, including for example, homeostatic responses and inflammatory mechanisms that could influence brain functioning and neurodevelopment independently of anesthesia. (25) The observed associations may also be attributable to any of several factors strongly conflated with surgery and anesthesia. For example, as noted above, children with the longest durations of surgery/anesthesia were those with non-sagittal synostosis, who underwent longer and more difficult surgeries at relatively older ages with concomitantly thicker skull bones. We adjusted for some of these factors (age and suture site) and conducted sub-analyses to rule out the contribution of others (e.g., existing differences among cases in *pre-surgery* neurodevelopmental status; total blood administered intra- and postoperatively). Although these adjustments did not appreciably affect estimates of exposure-outcome associations, the reliability of these analyses was limited by sample size. Additionally, there may be variables unmeasured in this research that are correlated with surgery length or anesthesia exposure and may account for the observed associations (e.g., structural complications related to the severity of cranial deformation).

The observed inverse correlations between exposures and neurodevelopment suggest that infants with SSC undergoing extremely long surgeries (> 7 hours) may be at considerably higher risk of subsequent delayed development, whether due to anesthesia exposures or not. Even lacking an understanding of the possible causal mechanisms, the development of such

infants should be monitored closely, with consideration of referral for neurodevelopmental screening and intervention.

The design of this study improves upon previous investigations of neurodevelopment as a surgical outcome by including a pre-surgery assessment of neurodevelopment, direct testing by trained psychometrists, and adjustment for several potential confounders. However, there are several limitations. As already noted, the study sample was relatively small, based at a single medical center, and restricted to children with SSC, a group for which there is no comparable group of infants undergoing non-craniofacial procedures. The absence of a non-craniofacial group limits the generalization of our findings to children with other indications for surgery. Although associations between exposures and neurodevelopmental outcomes persisted after adjustments for various confounders and other covariates as described above, these results should be regarded as tentative given the limited sample size and the possibility of unmeasured confounders.

Nevertheless, the observed inverse associations between neurodevelopment and duration of anesthesia-surgery exposures among infants with SSC should be considered and studied further. Previous investigations have suggested that a single brief exposure to surgical anesthesia in young children may not affect neurobehavioral development,(18,22,23) while multiple such exposures may.(19) This investigation, despite its limitations, introduces the possible neurodevelopmental effects of single, *prolonged* exposures to surgery and anesthesia in children with SSC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographic characteristics among children with single suture craniosynostosis

Demographic characteristic	Total Cases	
	<i>Number</i>	<i>Percent</i>
Total	70	100.0
Gender		
Female	27	38.6
Male	43	61.4
Age group		
< 6 months	25	35.7
6-9 months	24	34.3
9 months	21	30.0
Race		
Non-white	15	21.4
White	55	78.6
SES category¹		
I (high)	16	22.9
II	32	45.7
III	14	20.0
IV	7	10.0
V (low)	1	1.4
Suture site		
Sagittal	34	48.6
Metopic	17	24.3
Unicoronal	15	21.4
Lambdoid	4	5.7
Surgery²		
Frontal-orbital advancement	33	47.1
Total vault	2	2.9
Posterior vault modified pi	29	41.4
Posterior vault switch	4	5.7
Position during surgery		
Supine	39	55.7
Prone	31	44.3
ASA category³		
1	34	48.6
2	35	50.0
Pre-surgery weight (kg)		
4-<10	51	72.9
10+	19	27.1

¹Based on four-factor Hollingshead Index

²One subject was missing the type of surgery performed and one subject had anterior cranial vault reconstruction

³One subject was missing ASA category

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Table 2

Distribution of surgical and anesthesia-related variables among single-suture craniosynostosis patients

	<i>¹</i> n	Median	Mean	SD
<i>Surgery</i>				
Total surgical time (minutes)	70	245.0	238.5	93.9
Total red blood cells intra-+ postop (ml/kg)	70	35.0	40.4	19.5
Total red blood cells intraop (ml/kg)	69	28.8	34.1	16.1
Total platelets intra-+ postop (ml/kg)	2	11.9	11.9	11.4
Total platelets intraop (ml/kg)	1	6.3	6.3	0.0
Total fresh frozen plasma intra-+ postop (ml/kg)	45	12.5	21.0	19.0
Total fresh frozen plasma intraop (ml/kg)	25	13.7	19.6	13.3
<i>Anesthesia</i>				
Anesthesia duration (minutes)	70	333.5	335.4	96.3
Total amount of inhaled anesthetic (MAC minutes)	70	155.6	159.9	87.5
Total amount of sevoflurane (MAC minutes)	27	101.3	132.9	99.4
Total amount of isoflurane (MAC minutes)	49	138.8	155.2	85.4
Any lorazepam (yes/no)	11			
Any midazolam (yes/no)	21			
Total propofol intra-+postop (mg/kg)	40	4.4	9.9	14.6
<i>Opioids (total intra-op)²</i>				
Morphine (mcg/kg)	30	152.0	225.1	194.3
Fentanyl (mcg/kg)	52	8.9	10.1	6.9
Remifentanyl (mcg/kg)	31	78.0	83.9	44.3
<i>Opioids (total intra- + postop)²</i>				
Morphine (mcg/kg)	69	643.9	734.1	429.1
Fentanyl (mcg/kg)	52	9.5	10.3	6.8
Remifentanyl (mcg/kg)	31	78.0	83.9	44.3
<i>Hospital stay</i>				
Time to discharge from ICU (days)	70	1.0	1.4	0.6
Time to discharge from hospital (days)	70	3.0	3.4	1.0

¹ Number exposed (i.e. non-zero) among those seen for neurodevelopmental testing at age 36 months² No data on sufentanyl, alfentanil, or "other" categories of opioids SD-standard deviation

Table 3

Distribution of neurodevelopmental scores, pre-surgery and at 36 months, among children with single-suture craniosynostosis

	Pre-Surgery ¹		36 months		
	n	Mean	SD	Mean	SD
<i>Bayley Scales of Infant Development</i>					
Mental Development Index	70	88.6	10.3	89.6	15.2
Psychomotor Development Index	69	84.4	12.1	88.5	14.4
<i>Preschool Language Scale</i>					
Receptive Communication	67	90.7	14.4	96.7	16.2
Expressive Communication	66	95.5	14.3	94.2	14.5

SD-Standard deviation

¹Pre-surgery means are based only upon the infants for whom 36-month data were also available

Table 4

Distribution of adverse outcomes among children with single-suture craniosynostosis

Surgical outcome	Total Cases	
	Number	Percent
Total	70	100.0
Intraoperative Events & Complications		
<i>Low O2 Saturation (<80%)</i>	1	1.4
<i>Low Hematocrit (25 or less)</i>	45	64.3
<i>Low PH/acidosis (7.20 or less)</i>	2	2.9
<i>Low Glucose (<60)</i>	0	0.0
<i>Laboratory Coagulopathy</i>	2	2.9
<i>Clinically Significant Venous Air Embolism</i>	2	2.9
<i>Hypothermia</i>	7	10.0
<i>Hypotension</i>	1	1.4
<i>Cardiac Arrest</i>	0	0.0
<i>Complete Extubation</i>	1	1.4
<i>Other *</i>	2	2.9
<i>Any Intraoperative Complication</i>	50	71.4
Postoperative Events (24 Hrs after surgery)		
<i>Unplanned Extubation</i>	0	0.0
<i>Respiratory Failure</i>	1	1.4
<i>Hypotension</i>	0	0.0
<i>Clinically Significant Venous Air Embolism</i>	0	0.0
<i>Seizures</i>	1	1.4
<i>Abnormal CT Scan</i>	1	1.4
<i>Sepsis</i>	0	0.0
<i>Laboratory Coagulopathy</i>	19	27.1
<i>Other **</i>	2	2.9
Postoperative Events (during hospital stay)		
<i>Re-admit to ICU</i>	1	1.4
<i>Respiratory failure</i>	0	0.0
<i>Seizures</i>	0	0.0
<i>Sepsis</i>	0	0.0
<i>Other ***</i>	3	4.3
<i>Any Postoperative Complication</i>	23	32.9
<i>Any Intra- or Postoperative Complication</i>	57	81.4

* Other adverse intraoperative events: bradycardia without hypotension responsive to atropine (1); transient hypotension with EKG ST changes responsive to volume resuscitation (1)

** Other adverse events during first 24 postoperative hours: apnea following morphine bolus responsive to Narcan (1); bradycardia, hypoventilation responsive to bag-mask ventilation (1)

*** Other adverse events after first 24 postoperative hours: readmission POD 4 with fever and anemia (1); transient elevated liver function tests (1); scalp hematoma drained in the ICU with sedation (1)

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Adjusted linear regression association between 36-month neurodevelopment scores and anesthesia and surgery-related exposures among children with single-suture craniosynostosis

Table 5

Characteristic	Bayley Scales of Infant Development					Preschool Language Scale				
	Mental Development Index n=70					Receptive Communication n=67				
	<i>beta</i> ¹	95% CI ²	<i>p</i> -value	<i>beta</i> ¹	95% CI ²	<i>beta</i> ¹	95% CI ²	<i>p</i> -value	<i>beta</i> ¹	95% CI ²
Total surgical time (30 min)	-1.7	-4.0	0.5	-2.8	-4.6	-1.0	-4.4	0.3	-0.2	-2.4
Anesthesia duration (30 min)	-2.5	-4.3	0.009	-2.9	-4.3	-1.5	-4.3	0.007	-1.1	-3.0
Total amount of inhaled anesthetic (30 MAC min)	-1.5	-2.8	0.03	-0.9	-2.2	0.4	-3.2	0.02	-1.5	-3.1

¹ Adjusted for age at surgery (continuous) and suture site (sagittal, metopic, unicoronal, and lambdoid as indicator variables)

² Using robust standard error estimates

Table 6

Adjusted linear regression association between 36-month neurodevelopment scores and anesthesia and surgery-related exposures by suture site among children with single-suture craniosynostosis

	Bayley Scales of Infant Development						Preschool Language Scale																	
	Mental Development Index n=34, 36 ³						Psychomotor Development Index n=33, 36 ³						Receptive Communication n=33, 35 ³						Expressive Communication n=32, 34 ³					
	<i>I</i> <i>beta</i> ¹	95% <i>CI</i> ²	<i>p</i> -value	<i>I</i> <i>beta</i> ¹	95% <i>CI</i> ²	<i>p</i> -value	<i>I</i> <i>beta</i> ¹	95% <i>CI</i> ²	<i>p</i> -value	<i>I</i> <i>beta</i> ¹	95% <i>CI</i> ²	<i>p</i> -value	<i>I</i> <i>beta</i> ¹	95% <i>CI</i> ²	<i>p</i> -value	<i>I</i> <i>beta</i> ¹	95% <i>CI</i> ²	<i>p</i> -value						
Sagittal																								
Total surgical time (30 min)	-0.1	-2.1	1.8	0.89	-2.9	-5.7	0.0	0.06	-1.3	-4.3	1.7	0.40	1.3	-0.7	3.4	0.21								
Anesthesia duration (30 min)	-0.6	-2.1	1.0	0.49	-3.5	-5.9	-1.1	0.008	-1.3	-4.0	1.5	0.37	0.6	-1.2	2.3	0.54								
Total amount of inhaled anesthetic (30 MAC min)	-0.3	-2.1	1.5	0.77	-0.5	-2.7	1.6	0.64	-1.6	-4.4	1.1	0.25	-1.8	-3.8	0.1	0.07								
Non-Sagittal																								
Total surgical time (30 min)	-2.8	-6.1	0.5	0.11	-2.7	-5.3	-0.2	0.04	-2.4	-5.2	0.5	0.11	-1.2	-4.1	1.6	0.41								
Anesthesia duration (30 min)	-3.9	-6.5	-1.3	0.006	-2.8	-4.9	-0.8	0.01	-3.3	-5.7	-0.8	0.01	-2.1	-4.7	0.6	0.14								
Total amount of inhaled anesthetic (30 MAC min)	-1.9	-3.6	-0.2	0.04	-1.1	-2.7	0.6	0.21	-1.8	-3.6	-0.1	0.05	-1.3	-3.5	0.9	0.26								

¹ Adjusted for age at surgery (continuous)

² Using robust standard error estimates

³ N reported as sagittal, non-sagittal