Cognitive Outcome After Spinal Anesthesia and Surgery During Infancy

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BACKGROUND: Observational studies on pediatric anesthesia neurotoxicity have been unable to distinguish long-term effects of general anesthesia (GA) from factors associated with the need for surgery. A recent study on elementary school children who had received a single GA during the first year of life demonstrated an association in otherwise healthy children between the duration of anesthesia and diminished test scores and also revealed a subgroup of children with "very poor academic achievement" (VPAA), scoring below the fifth percentile on standardized testing. Analysis of postoperative cognitive function in a similar cohort of children anesthetized with an alternative to GA may help to begin to separate the effects of anesthesia from other confounders.

METHODS: We used a novel methodology to construct a combined medical and educational database to search for these effects in a similar cohort of children receiving spinal anesthesia (SA) for the same procedures. We compared former patients with a control population of students matched by grade, gender, year of testing, and socioeconomic status.

RESULTS: Vermont Department of Education records were analyzed for 265 students who had a single exposure to SA during infancy for circumcision, pyloromyotomy, or inguinal hernia repair. Exposure to SA and surgery had no significant effect on the odds of children having VPAA. (mathematics: $P = 0.18$; odds ratio 1.50, confidence interval (CI), 0.83–2.68; reading: $P = 0.55$; odds ratio = 1.19, CI, 0.67–2.1). There was no relationship between duration of exposure to SA and surgery and performance on mathematics ($P = 0.73$) or reading ($P = 0.57$) standardized testing. There was a small but statistically significant decrease in reading and math scores in the exposed group (mathematics: $P = 0.03$; reading: $P = 0.02$).

CONCLUSIONS: We found no link between duration of surgery with infant SA and scores on academic achievement testing in elementary school. We also found no relationship between infant SA and surgery with VPAA on elementary school testing, although the CIs were wide. (Anesth Analg 2014;119:651–60)

Despite intensive investigation, the clinical significance of anesthetic neurotoxicity in children remains uncertain. Laboratory evidence indicates that the administration of γ-aminobutyric acid agonist and *N*-methyl-D-aspartate antagonist medications to young animals during periods of rapid synaptic growth causes widespread central nervous system (CNS) damage. Administration of these drugs to species ranging from nematodes to subhuman primates produces dose-dependent neuronal apoptosis and dendritic cell damage. Behavioral changes characteristic of impaired CNS learning and memory appear to correlate with the histological evidence. There is increasing concern that these effects may occur at doses that are clinically relevant for humans.[1–10]

Translation of this animal work to humans has proven problematic. In the absence of randomized controlled trials, observational epidemiological studies have informed the discussion. A number of studies have demonstrated an association between general anesthesia and subsequent decrements in cognitive ability, while several studies have shown no effect.[11–20] These studies have used a variety of approaches to generate cohorts of children exposed to general anesthesia. Accordingly, these studies vary widely in the demographics of the exposed patients, types of surgery, and age at exposure, as well as surrogate end points for the assessment of CNS dysfunction.[12,14,15,20] Recent editorials highlight the difficulties in the construction and interpretation of these studies.[21,22]

The central confounding factor in previous clinical studies is the inability to separate the need for surgery and any potential influence of the surgical procedure from the effects of general anesthesia. Because elective surgery is not performed on infants, it has been postulated that the requirement for surgery at a young age may be a marker for children predestined for cognitive dysfunction later in life.[23–25] In this hypothesis, exposure to anesthesia and surgery is correlated but not causal. Because of the lack of suitable control populations, it appears unlikely that epidemiological studies that only examine children exposed to general anesthesia will isolate the potential impact of anesthetic exposure.

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Spinal anesthesia is an alternative to general anesthesia for a variety of surgical procedures in infants. Although less commonly used than general anesthesia, it has an established record of safety and has not been implicated in animal studies of neurotoxicity.[26–32] Analysis of cognitive function of children exposed to spinal anesthesia and surgery may play a role in our understanding of the potential risk of neurotoxicity of general anesthetics. In addition, because infant spinal anesthesia is used in a number of centers, a preliminary examination of the long-term outcome of children anesthetized with regional anesthesia is needed.

We hypothesized that this analysis would be most relevant if it used similar patient cohorts and outcome measures as previously reported studies examining cognitive outcome of children exposed to general anesthesia. Recently, Block et al.[12] studied a cohort of children in Iowa who underwent a single general anesthetic in the first year of life for 3 relatively minor surgical procedures not thought to be associated with later cognitive delay: circumcision, pyloromyotomy, and inguinal hernia repair. After seeking parental permission, they obtained access to results of standardized achievement testing and discovered 2 findings of particular concern. In otherwise healthy children, duration of exposure to anesthesia and surgery correlated negatively with test score performance. In addition, they discovered a much larger than expected subgroup of children with "very poor academic achievement" (VPAA), scoring below the fifth percentile. Because of the potential economic, academic, and public health consequences of this finding, we chose to study VPAA as our primary outcome measure.

At Vermont Children's Hospital, infants who require these same surgical procedures are routinely managed with spinal rather than general anesthesia. The current study explores the relationship of exposure to spinal anesthesia and surgery during infancy to subsequent performance on standardized achievement testing in elementary school. To reduce selection bias, produce the largest possible patient cohort, and construct an appropriately matched control population, we used a novel methodology to construct a combined medical and educational database.

METHODS

Identification of Patient Cohort

Since 1979, demographic and intraoperative data concerning all patients younger than 1 year undergoing spinal anesthesia at Vermont Children's Hospital have been entered into a computerized database entitled the Vermont Infant Spinal Registry (VISR). IRB approval was obtained for the following process under which medical and educational records were cross-matched in a deidentified manner.

The VISR database was queried for all infants undergoing spinal anesthesia for inguinal hernia repair, pyloromyotomy, and circumcision who were born between January 1, 1989, and August 31, 2003, at a gestational age of 28 weeks or more. This list was cross-matched with the hospital billing database to produce a list of patients who were Vermont residents at the time of their infant surgery and potentially eligible to take a series of standardized achievement tests administered in Vermont during the years 2000 to 2011. Medical records maintained at Vermont Children's Hospital were then reviewed by 1 of the 2 investigators (RKW and AFF). Patients who had subsequent surgery or other procedures requiring anesthesia in the first 5 years of life were excluded from analysis. Data from the patients' medical records were extracted and analyzed to determine patient ASA physical status, length of surgery, and the presence of preexisting CNS conditions (Table 1, modified from Block et al.[12]). Data from the VISR database were examined for patient gender, gestational age, postconceptual age at time of surgery, birthweight, weight at time of surgery, type of surgery, and need for supplemental IV sedation during surgery.

Matching of Patient Data with School Records

During the years 2000 to 2011, students in public school in Vermont were required to take either the New Standards Reference Examination achievement tests in reading, writing, and mathematics in grades 4, 8, and 10 (2000–2006) or the New England Common Assessment Program examination in grades 3, 4, 5, 6, 7, 8, and 11 (2005–2011). Results of these examinations, along with information concerning the student's need for an individual education plan (IEP), are maintained in a secure database by the Vermont Department of Education (VDOE).

Access to these data is restricted by provisions of The Family Educational Rights and Privacy Act (FERPA) and the Health Insurance Portability Act (HIPAA). FERPA is a federal statute governing access to educational records to maintain the privacy of the individual student's educational data. HIPAA protects the privacy of individually identifiable patient health information. Legal consultation was obtained to determine a methodology under which access to our cohort's educational records could be obtained while maintaining confidentiality of both patient and student information under FERPA and HIPAA regulations. Recent changes to FERPA language have facilitated the establishment of protocols that enable the matching of education data and other data that have been gathered on individuals and deidentified for analysis.[33] The deidentified nature of this process allowed us to obtain educational data without attrition due to difficulties in locating former patients and/or obtaining parental consent. The following protocol was established

Table 1. List of Preexisting Central Nervous System (CNS) Conditions

1	Seizure disorder (nonfebrile)
2	Surgery requiring cardiac bypass
3	Hydrocephalus
4	Microcephaly
5	Any type of intracranial hemorrhage
6	CNS infections
7	Stroke
8	Congenital syndromes associated with cognitive delay
9	Cleft lip or palate
10	Other congenital anomalies or deformities of skull, face, or jaw
11	Meningomyelocele/myelomeningocele
12	Use of ECMO
13	ARDS
14	Birth asphyxia
15	Miscellaneous brain diseases or conditions causing neurologic deficits
16	History of auditory problems or visual problems

CNS = central nervous system; ECMO = extracorporeal membrane oxygenation; ARDS = acute respiratory distress syndrome.

by counsel representing the University of Vermont and the VDOE. A deidentified, integrated medical, and educational research (DIMER) database was constructed by combining medical data with educational data from the VDOE. This matching process was conducted entirely on the premises of the VDOE. Names and dates of birth of the patient cohort were given to personnel of the VDOE, who matched them with preexisting student identifications. Once the data were matched, an arbitrary identification number was assigned to the individuals, and all identifiers such as names, dates of birth, and VDOE student identifications were stripped from the data. This DIMER database was used for all subsequent analyses. A confidentiality protocol was signed, which permitted one of the investigators (DH) to have access to the identified student record data to confirm the integrity of the matching. Data could only be reported for cell sizes larger than 10 individuals.

Data Analysis

To combine data across New Standards Reference Examination and New England Common Assessment Program achievement tests, grades, and test years, test scores were standardized by subtracting the statewide mean scores and dividing by the statewide standard deviation (SD) in scores, by student grade for each test year. Mathematics and reading scores were analyzed separately, and a minority of children only had test results available for 1 discipline. We constructed a control cohort of children matched with our exposed population by grade, gender, need for free or reduced school lunch, and year of examination. Three controls were created for each exposed subject. A frequency matching scheme was used based on a stratum of 4 criteria: gender, grade at first examination, year of examination, and need for free or reduced price school lunch. For n cases in a stratum, a random sample of $3 \times n$ controls were selected from the same stratum by SAS Proc Survey Select (SAS Institute Inc., Cary, NC).

We compared demographic characteristics of the patients whose academic data were recovered with those patients who had no data in VDOE files. t tests or χ^2 tests were used to compare characteristics of the exposed patients with achievement test scores in grades 3, 4, or 5 to the exposed patients with no test data for those grades.

Mixed model analysis via SAS Proc Glimmix was used to compare the proportion of students performing below the fifth percentile on the achievement tests, as well as the need for an IEP between the control and exposed populations, adjusting for the random effects of the strata of the matching scheme. Proc Glimmix was also used to calculate odds ratios with confidence intervals (CIs) for these comparisons.

We examined the effect of several univariate factors that could potentially affect academic performance. t tests or χ^2 tests were used to compare duration of surgery, birth weight, gestational age, age at surgery, surgery type, ASA physical status, and use of supplemental intraoperative sedation between those exposed patients performing below the fifth percentile on the tests, with those scoring at or above the fifth percentile.

Mixed model analysis, via SAS Proc Mixed, was used to compare mean achievement test scores between the exposed and control populations, adjusting for the random effects of the strata of the matching scheme. The Pearson product moment correlation coefficient was calculated to determine the effect on test scores for the exposed patients from the following factors: birth weight, gestational age, postconceptual age at surgery, and duration of surgery. t test analysis was calculated to examine the effect on test scores from the presence of preexisting CNS conditions, need for mechanical ventilation at any time before surgery, and the need for supplemental sedation. Analysis of variance was used to compare test scores by type of surgery. All statistical tests were 2-sided, using $P < 0.05$ as the criterion for statistical significance.

The primary outcome was the likelihood of children scoring below the fifth percentile. Secondary outcomes were the need for an IEP, mean reading score, and mean math scores. We used the entire population of children exposed to spinal anesthesia that was available for examination; consequently, an a priori power analysis was not performed.

Eligibility for a free or reduced price school lunch is the primary metric used by the VDOE and all 50 states as an indicator of socioeconomic status for individual students, schools, and school districts. To understand the effect of socioeconomic status on academic achievement in our cohort, we compared the presence or absence of free or reduced school lunch status (at the level of each student) with test score performance. We also compared the odds of having VPAA for all students in grades 3, 4, or 5 in the Vermont public school system with test scores during the final year of our study (2011).

RESULTS

Demographics and Data Attrition

We identified 356 children born in Vermont between January 1, 1989, and August 31, 2003, who received spinal anesthesia for pyloromyotomy, circumcision, or inguinal hernia repair, with no further exposure to surgery or anesthesia at Vermont Children's Hospital in their first 5 years of life. Cross-matching with records at VDOE recovered academic data for 286 (80.3%) patients. Two hundred sixty patients had test scores in grades 3, 4, or 5. Twenty-one patients had test scores available only for grades 7, 8, 10, or 11. Another 5 patients had blank test scores in all grades and the need for an IEP recorded. Demographic data for the 265 patients who had elementary school data available (test results and/or need for an IEP) are found in Table 2. Educational data were not found for 91 patients. Demographic data for these students are presented in Table 2. No demographic differences were found between students with and without test data retrieved.

We were able to report on all data available within the VDOE files with the exception of race. Because of the relatively small percentage of nonwhite students in Vermont during the time period of this study, the minimum cell size restriction of 10 prevented us from searching for effects of race.

Students with Very Poor Academic Achievement

Figures 1 and 2 show the distribution of reading and math test scores of both exposed and control populations.

Table 2. Demographic Characteristics of Children Exposed to Spinal Anesthesia: Comparison of Groups with Data Recovered Versus No Department of Education Records Retrieved

Characteristic	Patients with test scores in grades 3 to 5 *n* = 265	Patients with no data/no test scores in grades 3 to 5 *n* = 91	*P*
Gender	86% male	89% male	0.52
Free/reduced hot lunch	52% yes	N.A.	
Surgery type			
Inguinal hernia repair	76%	80%	0.15
Pyloromyotomy	18%	11%	
Circumcision	5%	9%	
Preexisting central nervous system condition	4%	0%	0.06
ASA physical status			
1	64%	73%	0.19
2	34%	27%	
3	2%	0%	
	n = 261	*n* = 82	
Birth weight, mean (g), SD	2848 ± 950	3046 ± 935	0.10
Gestational age, mean, SD	37.5 ± 3.7	37.4 ± 3.3	0.85
Age at surgery since conception, mean (wk), SD	48 ± 8	49 ± 9	0.43
Duration of surgery, mean, (min), SD	38.2 ± 13.5	40.7 ± 16.1	0.19

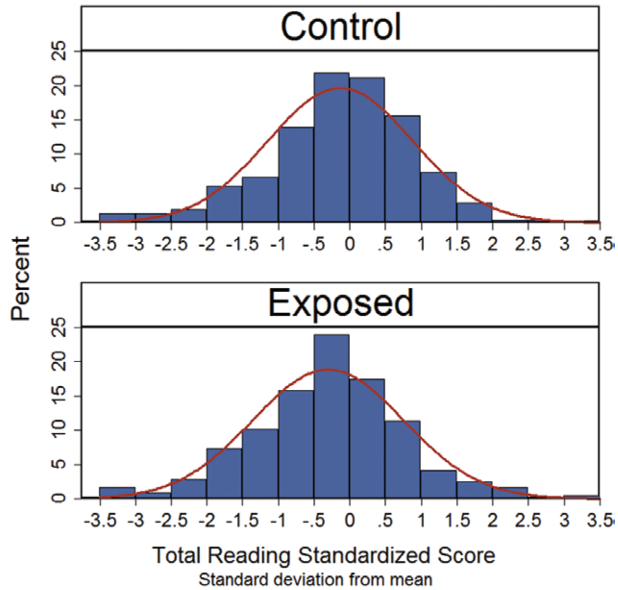

Figure 1. Distribution of standardized reading achievement test scores.

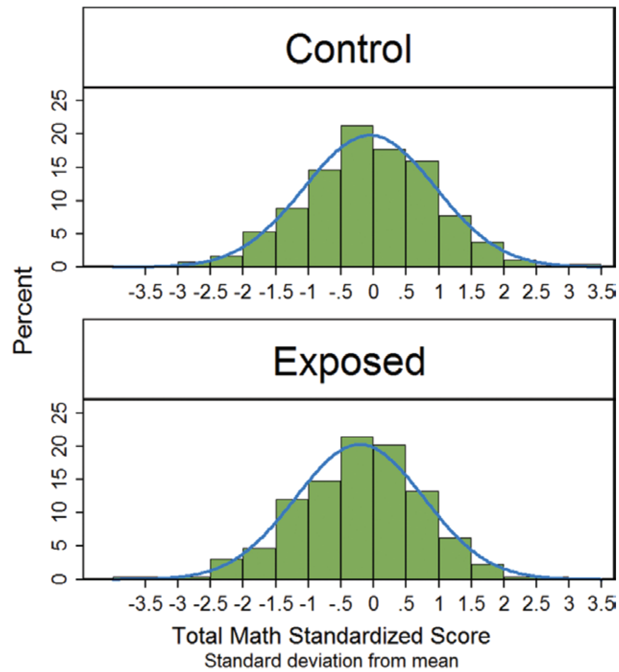

Figure 2. Distribution of standardized mathematics achievement test scores.

Q-Q plots of exposed and control patients are shown in Figures 3 and 4. We searched for evidence of a subgroup of children with VPAA. There was no evidence of an increased number of very poor achievers in the exposed group when compared with the control population, which was adjusted for gender, free or reduced price lunch, grade, and year of testing (Table 3). Student *t* test analysis was used to search for factors influencing VPAA. No relationship was found between VPAA and mean duration of surgery, birthweight, age at surgery, type of surgery, or ASA physical status (Tables 7 and 8). Socioeconomic status as defined by the need for free or reduced price school lunch had a marked effect on the likelihood of students having VPAA.

Need for an IEP

Student records were reviewed for the presence of an IEP at any point in time. Mixed model analysis revealed no statistically significant difference in need for an IEP between exposed patients (26.2%) compared with controls (20.8%, $P = 0.15$); odds ratio 1.28, 95% CI, (0.91–1.79).

Effects on Mean Test Scores

Comparison of the exposed population with controls revealed small but statistically significant differences in mean test scores (Table 4). The Cohen *d* effect size for the difference in both reading and math scores was 0.16. Duration of surgery had no effect on test scores for either math or reading examinations. Similarly, no effect was noted due to birthweight, gestational age, or age at time of surgery (Table 5). *t* test analysis revealed no relationship between test scores and type of surgery, presence of preexisting CNS

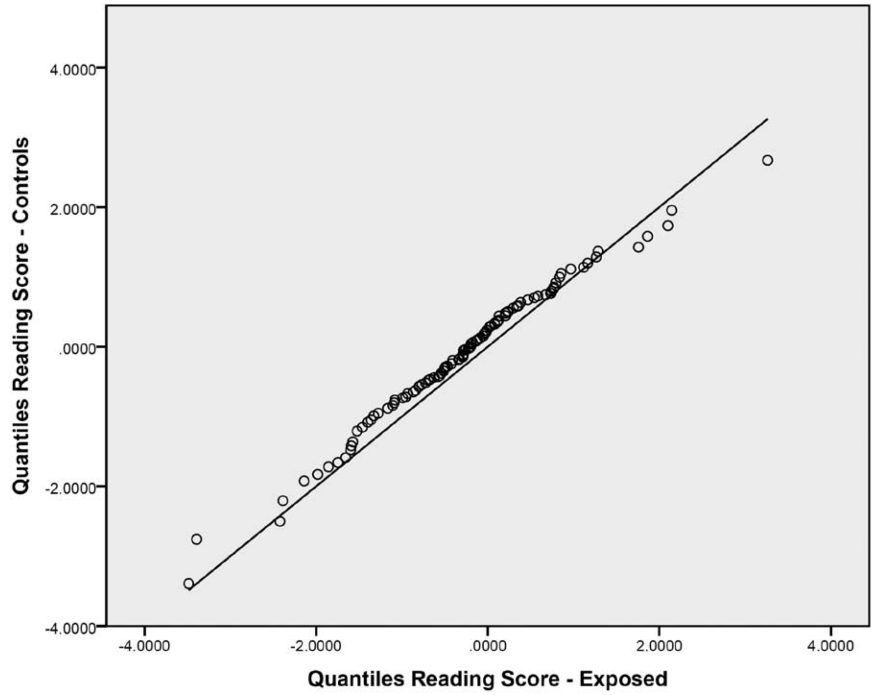

Figure 3. Q-Q plot of exposed versus controls on reading achievement testing.

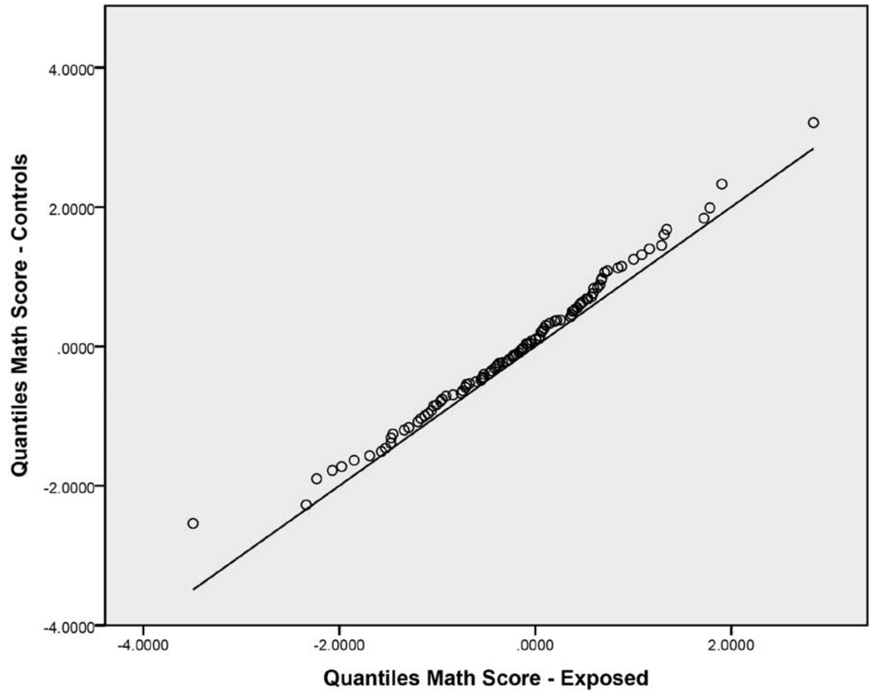

Figure 4. Q-Q plot of exposed versus controls on mathematics achievement testing.

Table 3. Students Scoring Below the Fifth Percentile on a Vermont School Standardized Achievement Test

All students	Exposed patients	Controls	*P* adjusted for strata	OR (95% CI)
Total math	7.0% (18/257)	4.8% (37/771)	0.18	1.50 (0.83–2.68)
Total reading	7.3% (18/246)	6.2% (46/738)	0.55	1.19 (0.67–2.10)

conditions, use of supplemental intraoperative sedation, or need for mechanical ventilation before surgery (Table 9).

We analyzed test data for 17,962 Vermont public school system students with either reading or math scores in grades 3, 4, or 5 during 2011. We found a strong relationship between the presence of free or reduced price school lunch and the odds of having VPAA, as well as decrements in mean test scores (Table 6).

Table 4. Comparison of Mean Test Scores Between Exposed and Control Populations: Least Squares Adjusted Mean ± SE[a]

	Exposed patients	Controls	*P*
Total math	−0.20 ± 0.07 (*n* = 257)	−0.04 ± 0.05 (*n* = 771)	0.03
Total reading	−0.25 ± 0.08 (*n* = 246)	−0.08 ± 0.06 (*n* = 738)	0.02

[a]Adjusted for gender, free/reduced lunch, grade, and year of test.

Table 5. Pearson Product Moment Correlation for Effects on Mean Test Scores

	Total reading score	Total math score
Duration of surgery (index procedure)	*N* = 246; *r* = −0.04; *P* = 0.57	*N* = 257; *r* = −0.02; *P* = 0.73
Birth weight	*N* = 242; *r* = 0.00; *P* = 0.95	*N* = 253; *r* = 0.10; *P* = 0.12
Gestational age	*N* = 246; *r* = −0.05; *P* = 0.47	*N* = 257; *r* = 0.02; *P* = 0.70
Age at surgery since conception (wk)	*N* = 246; *r* = −0.02; *P* = 0.75	*N* = 257; *r* = −0.05; *P* = 0.43
Age at surgery (d)	*N* = 246; *r* = 0.00; *P* = 0.99	*N* = 257; *r* = −0.07; *P* = 0.30

Table 6. Effect of Free School Lunch Status on Elementary School Achievement Test Performance for All Students in the Vermont Public School System During 2011

Free or reduced lunch	Yes	No	*P*	Odds ratio (95% CI)
% VPAA–reading	7.5% (587/7870)	1.9% (191/10048)	<0.001	4.16 (3.52–4.91)
% VPAA–math	8.2% (641/7793)	2.4% (235/9970)	<0.001	3.71 (3.19–4.32)
Reading test score (mean ± SD)	−0.26 ± 0.86	0.20 ± 1.05	<0.001	
Math test score (mean ± SD)	−0.24 ± 0.92	0.18 ± 1.02	<0.001	

VPAA = very poor academic achievement.

Table 7. Factors Affecting Very Poor Academic Achievement on Reading Testing

Total reading score <5th percentile	Yes (mean ± SD)	No (mean ± SD)	*P* (*t* test)
Duration of surgery (index procedure) (min)	41.8 ± 12.1 (*n* = 18)	37.8 ± 13.5 (*n* = 228)	0.22
Free or reduced lunch	77.8% (14/18)	48.7% (111/228)	0.02
Birth weight (g)	2989 ± 720 (*n* = 18)	2865 ± 962 (*n* = 224)	0.59
Gestational age (wk)	38.4 ± 2.4 (*n* = 18)	37.4 ± 3.8 (*n* = 228)	0.14
Age at surgery since conception (wk)	49.1 ± 10.1 (*n* = 18)	48.2 ± 8.4 (*n* = 228)	0.67
Age at surgery (d)	75 ± 68 (*n* = 18)	76 ± 55 (*n* = 228)	0.98
			P **(χ^2)**
Surgery type	0% Circ; 83% IHR; 17% PYLORO	5% Circ; 75% IHR; 19% Pyloro	0.56
ASA physical status of II or III	38.9% (7/18)	35.1% (80/228)	0.75
Supplemental intraoperative sedation	33.3% (6/18)	26.4% (60/227)	0.53

CIRC = circumcision; PYLORO = pyloromyotomy; IHR = inguinal hernia repair.

Table 8. Factors Affecting Very Poor Academic Achievement on Mathematics Testing

Total math score <5th percentile	Yes (mean ± SD)	No (mean ± SD)	*P* (*t* test)
Duration of surgery (index procedure) (min)	38.4 ± 11.8 (*n* = 18)	38.3 ± 13.7 (*n* = 239)	0.97
Free or reduced lunch	83.3% (15/18)	49.0% (117/239)	0.005
Birth weight (g)	2790 ± 1002 (*n* = 18)	2873 ± 952 (*n* = 235)	0.72
Gestational age (wk)	38.1 ± 3.2 (*n* = 18)	37.5 ± 3.8 (*n* = 239)	0.50
Age at surgery since conception (wk)	49.5 ± 12.4 (*n* = 18)	48.1 ± 7.9 (*n* = 239)	0.63
Age at surgery (d)	80 ± 79 (*n* = 18)	74 ± 52 (*n* = 228)	0.76
			P **(χ^2)**
Surgery type	6% Circ; 67% IHR; 28% PYLORO	5% Circ; 77% IHR; 18% Pyloro	0.55
ASA physical status (II or III)	50.0% (9/18)	34.3% (82/239)	0.18
Supplemental sedation	44.4% (8/18)	24.8% (59/238)	0.07

CIRC = circumcision; PYLORO = pyloromyotomy; IHR = inguinal hernia repair.

DISCUSSION

Observational studies concerning the neurotoxicity of general anesthetic drugs in children have been unable to separate effects of the anesthetic from other confounding factors. This difficulty was summarized in a SmartTots consensus statement that concluded "…these studies had limitations that prevent experts from drawing conclusions on whether the harmful effects were due to the anesthesia or to other factors, including surgery, hospitalization, or preexisting conditions."[34] Our experimental design examined some of these limitations by exploring the cognitive outcome of children anesthetized with an alternative to general anesthesia not thought to be associated with neurotoxicity.

Table 9. Effects on Mean Test Scores

	Surgery type			
	Circ	IHR	Pyloro	*P* (anova)
Total math	−0.25 ± 0.68 (*n* = 14)	−0.20 ± 1.01 (*n* = 196)	−0.27 ± 0.95 (*n* = 47)	0.90
Total reading	−0.42 ± 0.74 (*n* = 12)	−0.30 ± 1.08 (*n* = 187)	−0.28 ± 1.06 (*n* = 47)	0.92
Central nervous system conditions		**Yes**	**No**	***P* (*t* test)**
Total math		−0.27 ± 1.07 (*n* = 9)	−0.21 ± 0.98 (*n* = 298)	0.86
Total reading		−0.39 ± 1.09 (*n* = 6)	−0.32 ± 1.05 (*n* = 240)	0.11
Supplemental sedation		**Yes**	**No**	
Total math		−0.34 ± 1.00 (*n* = 67)	−0.17 ± 0.98 (*n* = 189)	0.23
Total reading		−0.32 ± 1.19 (*n* = 66)	−0.30 ± 1.00 (*n* = 179)	0.91
Mechanical ventilation		**Yes**	**No**	
Total math Z-score		−0.16 ± 0.95 (*n* = 39)	−0.22 ± 0.99 (*n* = 218)	0.70
Total reading Z-score		−0.12 ± 0.78 (*n* = 37)	−0.33 ± 1.10 (*n* = 209)	0.16

Mean ± SD.
CIRC = circumcision; PYLORO = pyloromyotomy; IHR = inguinal hernia repair.

Recent work by Block et al.[12] found an association between duration of a single exposure to general anesthesia and surgery during infancy with decreased performance on standardized testing in otherwise healthy children. In addition, their group demonstrated an association between exposure to general anesthesia and surgery with an increased number of children with VPAA. Fourteen percent of otherwise healthy patients scored below the fifth percentile on Iowa academic achievement tests. Our results differed substantially. In a cohort of patients exposed to spinal anesthesia for the same types of surgery, we found no relationship between the duration of exposure to spinal anesthesia and surgery with performance on standardized testing. When we compared these patients with a matched control population, we found no difference in odds of the number of children with VPAA after exposure to spinal anesthesia and surgery.

Our results should be viewed as preliminary, and appropriate caution must be used in their interpretation relative to those of Block et al.[12] We did not have a cohort of children exposed to general anesthesia as a comparative group. In addition, unknown potential differences in patient demographics, surgical techniques, and testing methodologies limit direct comparison. Our methodology reduced selection bias and difficulties contacting former patients, producing a substantial (80%) capture rate of data. In addition, we were able to construct a control population of children matched by grade, year of examination, gender, and socioeconomic status.

The importance of socioeconomic status on academic performance may be substantial. Socioeconomic status, as defined by the need for free or reduced price school lunch, had a marked effect on academic performance within the overall population of public school children in Vermont. In addition, within our study population, the presence or absence of free school lunch had a much more powerful effect on the odds of VPAA than did exposure to spinal anesthesia and surgery. This reinforces the importance of using an appropriately matched control population. The use of this or similar methodology to examine children previously exposed to general anesthesia would potentially be of value to other investigators. Because construction of the DIMER database was governed by federal statutes, this approach should be exportable to other states and jurisdictions.

Our results also suggest that the population of children presenting for surgery in the first year of life differs from the overall population in substantive ways that must be considered in analysis of children exposed to surgery and any type of anesthesia. There was a small decrease in adjusted reading and math scores in the group exposed to spinal anesthesia and surgery. In addition, although we found no significant difference in the number of children in the exposed group with VPAA, the CIs around the odds ratio of this effect are relatively wide. The wide CIs imply that the likelihood for an exposed student to have scored below the fifth percentile could have been anywhere from two-thirds the odds for a control student to 2 to 3 times higher.

It is possible that these results are related to a previously unrecognized effect from spinal anesthesia per se; however, this appears unlikely. Our study revealed no relationship between duration of exposure to spinal anesthesia and surgery with test scores. Furthermore, preclinical work has found no evidence of neurotoxicity from spinal anesthesia in young animals.[26,32]

It appears more likely that the decrement in mean scores and wide CIs for VPAA may be related to demographic factors in the surgical population that our control model could not account for. Our model controlled for gender, grade, year of examination, and socioeconomic status and is an improvement over comparing exposed patients to the entire population of students taking state-based achievement tests. However, prematurity, health status, maternal education, and birth weight are other known covariates that have substantial effects on academic achievement testing.[35,36] These factors could not be included in the model of our control group because they are not included in VDOE student records. Prematurity is likely to be the most significant missing factor, which differs between our exposed and control groups. During the time period of this study, 6.2% of births in Vermont were <37 weeks gestation compared with 29% of patients in our cohort.[37] This increased proportion of former premature infants may be expected to produce a decrement in mean test scores in the exposed population. The differences in mean scores between groups reached statistical significance. However, the absolute differences were small as were the Cohen *d* effect size. As such, the educational significance appears minimal. We saw no correlation between test scores and birthweight, age at surgery, or gestational age. The reason for this is uncertain but could be related to the small range seen in our mean test scores.

Because there is an acknowledged degree of subjectivity to the IEP designation process,[38,39] we chose not to use the need for an IEP as a primary outcome. However, we did compare the need for an IEP between the exposed and control populations in an effort to search for an overrepresentation of severely challenged children within the exposed population. We found no relationship between exposure to spinal anesthesia and surgery with the need for an IEP.

Limitations and Data Attrition

There are several limitations to our study. One limitation is that 20% of the exposed cohort did not have test scores available. Data for the missing patients may have been unavailable for a variety of reasons, including death or emigration away from Vermont, voluntary nonparticipation in standardized testing, or test score nonattainment.

Test score nonattainment has been a significant issue in several previous studies.[16,40] Consequently, we aggressively searched for evidence that exposed children may have been so severely affected that they were unable to take standardized tests and may have been missed by our analysis. We found that Vermont has a high rate of achievement testing (97%) for children within the public educational system, and most children with significant disabilities would have taken the examination, with accommodations if needed.[41] Although it is possible that some severely affected children would remain outside the public educational system and thus not be required to take tests, this is extremely unlikely because public school systems in Vermont have significantly greater resources for developmentally challenged students than are available in private or home schooling.

Death or emigration away from Vermont are other possible reasons for missing data within VDOE records. However, the most likely cause may be students who attended private schools or were home-schooled. During the time of this study, approximately 17% of Vermont school children were either home-schooled or attended private school.[42,43] These students are not required by law to undergo standardized testing, and avoidance of standardized testing is a frequently stated reason for alternative schooling.

We examined demographic data for the missing students to understand whether they were potentially a cohort of children who had a greater burden of disease and thus would be unlikely to perform well on standardized testing. This does not appear to be the case because all demographic data for the missing students appear similar to the cohort that was analyzed (Table 2). There were no patients with preexisting CNS conditions in the missing group.

Another limitation is that our exposed patients may have received subsequent exposure to general anesthesia. We reviewed medical records at Vermont Children's Hospital to eliminate those patients younger than 5 years who had other surgical procedures. Although it is possible that some of our cohort had subsequent exposure to general anesthesia at other facilities, this appears unlikely. Because of the distribution of pediatric surgical and anesthesia resources in our referral area, most exposed patients would have received subsequent surgical and anesthesia care at our facility and have records available to us. However, any undocumented exposure to general anesthesia would tend to bias results in the exposed group toward an anesthetic effect and away from our finding that exposure to spinal anesthesia and surgery has no effect on VPAA.

Another potential limitation is that during this study an undetermined number of children at our institution received general anesthesia for the index procedures. However, both the surgical and anesthesia teams at the University of Vermont have a strong preference for spinal anesthesia, particularly in infants with comorbidities.[29,44,45] Consequently, the number of children who received general anesthesia is very small and it is extremely unlikely that healthier children preferentially received spinal anesthesia.

Performance on group-administered academic achievement testing has been a useful measurement for analyzing cognitive function because of its objectivity, normal distribution, and interest to parents and educators.[12,16,40] However, group-administered testing is a relatively coarse assessment of cognitive function.[21] Individually administered neurocognitive assessments are likely to be more sensitive in determining any potential subtle deficits associated with the administration of anesthesia and surgery. Individualized neurocognitive follow-up examination of children previously exposed to regional anesthesia and surgery may add to our understanding of the relative roles of anesthesia exposure, patient demographics, and influence of the surgical procedure on postoperative cognitive function in children. Ideally, testing would be informed by previous work suggesting deficits in specific domains and would include groups of children exposed to both general and regional anesthesia.[17] Such studies would also prove useful in attempting to understand the long-term safety of regional anesthesia during infancy. Because the use of infant spinal anesthesia is a minority practice, the number of children previously exposed to spinal anesthesia and available for study is limited. However, in addition to our registry, there are smaller cohorts of children who received infant spinal anesthesia in Israel and during the GAS study.[46–48]

CONCLUSIONS

We found no link between duration of infant surgery under spinal anesthesia and performance on academic achievement testing in elementary school. We also found no relationship between infant spinal anesthesia and surgery with very poor performance on elementary school achievement testing, although the CIs were wide. Further study is needed to understand whether choice of anesthetic technique has an influence on cognitive function after surgery during infancy.

DISCLOSURES

Name: Robert K. Williams, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Robert K. Williams has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Ian H. Black, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Ian H. Black has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped analyze the data and write the manuscript.
Attestation: Diantha B. Howard has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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REFERENCES

1. Brambrink AM, Back SA, Riddle A, Gong X, Moravec MD, Dissen GA, Creeley CE, Dikranian KT, Olney JW. Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. Ann Neurol 2012;72:525–35
2. Cattano D, Young C, Straiko MM, Olney JW. Subanesthetic doses of propofol induce neuroapoptosis in the infant mouse brain. Anesth Analg 2008;106:1712–4
3. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003;23:876–82
4. Yu D, Jiang Y, Gao J, Liu B, Chen P. Repeated exposure to propofol potentiates neuroapoptosis and long-term behavioral deficits in neonatal rats. Neurosci Lett 2013;534:41–6
5. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. Anesth Analg 2008;106:1681–707
6. Gentry KR, Steele LM, Sedensky MM, Morgan PG. Early developmental exposure to volatile anesthetics causes behavioral defects in Caenorhabditis elegans. Anesth Analg 2013;116:185–9
7. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology 2010;112:834–41
8. Paule MG, Li M, Allen RR, Liu F, Zou X, Hotchkiss C, Hanig JP, Patterson TA, Slikker W Jr, Wang C. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. Neurotoxicol Teratol 2011;33:220–30
9. Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, Sun D, Baxter MG, Zhang Y, Xie Z. Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. Anesthesiology 2013;118:502–15
10. Creeley C, Dikranian K, Dissen G, Martin L, Olney J, Brambrink A. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth 2013;110 Suppl 1:i29–38
11. Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet 2009;12:246–53
12. Block RI, Thomas JJ, Bayman EO, Choi JY, Kimble KK, Todd MM. Are anesthesia and surgery during infancy associated with altered academic performance during childhood? Anesthesiology 2012;117:494–503
13. DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol 2009;21:286–91
14. DiMaggio C, Sun LS, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. Anesth Analg 2011;113:1143–51
15. Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics 2011;128:e1053–61
16. Hansen TG, Pedersen JK, Henneberg SW, Pedersen DA, Murray JC, Morton NS, Christensen K. Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. Anesthesiology 2011;114:1076–85
17. Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, Davidson A, Wood AJ, Li G, Sun LS. Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics 2012;130:e476–85
18. Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanić K, Welch TL, Olson MD, Hanson AC, Schroeder DR, Wilder RT, Warner DO. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc 2012;87:120–9
19. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009;110:796–804
20. Walker K, Halliday R, Holland AJ, Karskens C, Badawi N. Early developmental outcome of infants with infantile hypertrophic pyloric stenosis. J Pediatr Surg 2010;45:2369–72
21. Flick RP, Warner DO. A users' guide to interpreting observational studies of pediatric anesthetic neurotoxicity: the lessons of Sir Bradford Hill. Anesthesiology 2012;117:459–62
22. Crosby G, Davis PJ. General anesthesia in infancy is associated with learning disabilities-or not. Anesth Analg 2013;117:1270–2
23. Davidson AJ. Anesthesia and neurotoxicity to the developing brain: the clinical relevance. Paediatr Anaesth 2011;21:716–21
24. Hansen TG, Henneberg SW, Morton NS, Christensen K, Davidson AJ, Lee KJ, Hardy P, Wolf A. Pro-con debate: cohort studies vs the randomized clinical trial methodology in pediatric anesthesia. Paediatr Anaesth 2010;20:880–94
25. Hansen TG, Flick R; Danish Registry Study Group; Mayo Clinic Pediatric Anesthesia and Learning Disabilities Study Group. Anesthetic effects on the developing brain: insights from epidemiology. Anesthesiology 2009;110:1–3
26. Yahalom B, Athiraman U, Soriano SG, Zurakowski D, Carpino EA, Corfas G, Berde CB. Spinal anesthesia in infant rats: development of a model and assessment of neurologic outcomes. Anesthesiology 2011;114:1325–35
27. Krane EJ, Haberkern CM, Jacobson LE. Postoperative apnea, bradycardia, and oxygen desaturation in formerly premature infants: prospective comparison of spinal and general anesthesia. Anesth Analg 1995;80:7–13
28. Oberlander TF, Berde CB, Lam KH, Rappaport LA, Saul JP. Infants tolerate spinal anesthesia with minimal overall autonomic changes: analysis of heart rate variability in former premature infants undergoing hernia repair. Anesth Analg 1995;80:20–7
29. Williams RK, Adams DC, Aladjem EV, Kreutz JM, Sartorelli KH, Vane DW, Abajian JC. The safety and efficacy of spinal anesthesia for surgery in infants: the Vermont Infant Spinal Registry. Anesth Analg 2006;102:67–71
30. Sprung J, Flick RP, Wilder RT, Katusic SK, Pike TL, Dingli M, Gleich SJ, Schroeder DR, Barbaresi WJ, Hanson AC, Warner DO. Anesthesia for cesarean delivery and learning disabilities in a population-based birth cohort. Anesthesiology 2009;111:302–10

31. Flick RP, Lee K, Hofer RE, Beinborn CW, Hambel EM, Klein MK, Gunn PW, Wilder RT, Katusic SK, Schroeder DR, Warner DO, Sprung J. Neuraxial labor analgesia for vaginal delivery and its effects on childhood learning disabilities. Anesth Analg 2011;112:1424–31
32. Hamurtekin E, Fitzsimmons BL, Shubayev VI, Grafe MR, Deumens R, Yaksh TL, Walker SM. Evaluation of spinal toxicity and long-term spinal reflex function after intrathecal levobupivaciane in the neonatal rat. Anesthesiology 2013;119:142–55
33. Education USDo. Family educational rights and privacy act regulations. In: Education USDo, ed. Washington, DC: Federal Register, 2011:34 CFR Part 99, Subpart D
34. Consensus Statement on the Use of Anesthetics and Sedatives in Children. SmartTots, 2012. Available at: http://www.smarttots.org/resources/consensus.html. Accessed April 16, 2013
35. Noble KG, Fifer WP, Rauh VA, Nomura Y, Andrews HF. Academic achievement varies with gestational age among children born at term. Pediatrics 2012;130:e257–64
36. Fowler MG, Johnson MP, Atkinson SS. School achievement and absence in children with chronic health conditions. J Pediatr 1985;106:683–7
37. PRAMS and Preterm Birth. Department of Health and Human Services, 2006. Available at: http://www.cdc.gov/reproductivehealth/ProductsPubs/PDFs/Preterm%20Delivery%20FS.pdf. Accessed April 9, 2013
38. Algozzine B, Ysseldyke JE, Shinn M. Identifying children with learning disabilities: When is a discrepancy severe? J Sch Psychol 1982;20:299–305
39. Ysseldyke JE, Algozzine B, Shinn MR, McGue M. Similarities and differences between low achievers and students classified learning disabled. J Spec Educ 1982;16:73–85
40. Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K. Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: a nationwide cohort study. Paediatr Anaesth 2013;23:883–90
41. Hock M, State Testing Director, Vermont Department of Education, 2011
42. Demographics—numbers and growth. Available at: http://homeschooling.gomilpitas.com/weblinks/demographics.htm. Accessed April 9, 2013
43. Vermont Private Schools. Available at: http://www.privateschoolreview.com/state_private_schools/stateid/VT. Accessed April 9, 2013
44. Williams RK, McBride WJ, Abajian JC. Combined spinal and epidural anaesthesia for major abdominal surgery in infants. Can J Anaesth 1997;44:511–4
45. Williams RK, Abajian JC. High spinal anaesthesia for repair of patent ductus arteriosus in neonates. Paediatr Anaesth 1997;7:205–9
46. Kachko L, Simhi E, Tzeitlin E, Efrat R, Tarabikin E, Peled E, Metzner I, Katz J. Spinal anesthesia in neonates and infants - a single-center experience of 505 cases. Paediatr Anaesth 2007;17:647–53
47. Kachko L, Birk E, Simhi E, Tzeitlin E, Freud E, Katz J. Spinal anesthesia for noncardiac surgery in infants with congenital heart diseases. Paediatr Anaesth 2012;22:647–53
48. McCann ME, Bellinger D, Arnup S, De Graaff JC, Disma N, Withington DE, Morton N, Davidson AJ. The GAS Study: Perioperative Outcomes in an RCT Comparing Spinal and General Anesthesia for Infant Hernia Repair. In:. San Francisco, CA: American Society of Anesthesiologists Annual Meeting, 2013