Academic Performance in Adolescence after Inguinal Hernia Repair in Infancy

A Nationwide Cohort Study

Tom G. Hansen, M.D., Ph.D.,* Jacob K. Pedersen, M.Sc.,† Steen W. Henneberg, M.D., Ph.D.,‡ Dorthe A. Pedersen, M.Sc.,† Jeffrey C. Murray, M.D.,§ Neil S. Morton, M.D.,‖ Kaare Christensen, M.D., Ph.D., D.M.Sc.#

ABSTRACT

Background: Although animal studies have indicated that general anesthetics may result in widespread apoptotic neurodegeneration and neurocognitive impairment in the developing brain, results from human studies are scarce. We investigated the association between exposure to surgery and anesthesia for inguinal hernia repair in infancy and subsequent academic performance.

Methods: Using Danish birth cohorts from 1986–1990, we compared the academic performance of all children who had undergone inguinal hernia repair in infancy to a randomly selected, age-matched 5% population sample. Primary analysis compared average test scores at ninth grade adjusting for sex, birth weight, and paternal and maternal age and education. Secondary analysis compared the proportions of children not attaining test scores between the two groups.

Results: From 1986–1990 in Denmark, 2,689 children underwent inguinal hernia repair in infancy. A randomly selected, age-matched 5% population sample consists of 14,575 individuals. Although the exposure group performed worse than the control group (average score 0.26 lower; 95% CI, 0.21–0.31), after adjusting for known confounders, no statistically significant difference (−0.04; 95% CI, −0.09 to 0.01) between the exposure and control groups could be demonstrated. However, the odds ratio for test score nonattainment associated with inguinal hernia repair was 1.18 (95% CI, 1.04–1.35). Excluding from analyses children with other congenital malformations, the difference in mean test scores remained nearly unchanged (0.05; 95% CI, 0.00–0.11). In addition, the increased proportion of test score nonattainment within the exposure group was attenuated (odds ratio = 1.13; 95% CI, 0.98–1.31).

Conclusion: In the ethnically and socioeconomically homogeneous Danish population, we found no evidence that a single, relatively brief anesthetic exposure in connection with hernia repair in infancy reduced academic performance at age 15 or 16 yr after adjusting for known confounding factors. However, the higher test score nonattainment rate among the hernia group could suggest that a subgroup of these children are developmentally disadvantaged compared with the background population.

What We Already Know about This Topic

- Animal studies have raised concerns about the potential for neurocognitive impairment from general anesthesia in human newborns, but clinical studies are inconclusive.

What This Article Tells Us That Is New

- In more than 2,500 children who underwent inguinal hernia repair as infants in Denmark, academic test scores in ninth grade were not different than those of a randomly selected sample after adjusting for known confounders.

A SUBSTANTIAL number of neonates and infants receive anesthesia and surgery each year.[1] Based on the results of animal studies, concerns have been raised that anesthesia may be harmful for the developing human brain. In

* Consultant Pediatric Anesthesiologist, Department of Anesthesia and Intensive Care, Odense University Hospital, Denmark. † Research Assistant, Institute of Public Health–Epidemiology, University of Southern Denmark, Odense, Denmark. ‡ Consultant Pediatric Anesthesiologist, Department of Anesthesia, Juliane Marie Center, Copenhagen University Hospital–Rigshospitalet, Copenhagen, Denmark. § Professor, Institute of Public Health–Epidemiology, University of Southern Denmark, Odense, and Department of Pediatrics, Epidemiology and Biological Sciences, University of Iowa, Iowa City, Iowa. ‖ Consultant Pediatric Anesthesiologist, Department of Anesthesia, Royal Hospital for Sick Children, Yorkhill, Glasgow, United Kingdom. # Professor, Institute of Public Health–Epidemiology, University of Southern Denmark, Odense, and Department of Clinical Biochemistry and Pharmacology and Department of Clinical Genetics, Odense University Hospital.

Received from the Department of Anesthesia and Intensive Care, Odense University Hospital, and the Institute of Public Health–Epidemiology at the University of Southern Denmark, Odense, Denmark. Submitted for publication June 21, 2010. Accepted for publication November 22, 2010. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual scientific meeting of the Association of Paediatric Anaesthetists of Great Britain and Ireland, Glasgow, United Kingdom, May 13–14, 2010.

Address correspondence to Dr. Hansen: Department of Anesthesia & Intensive Care, Odense University Hospital, DK-5000 Odense C, Denmark. tomghansen@dadlnet.dk. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

 Anesthesiology 2011; 114:1076–85

the past decade, several animal studies have demonstrated that *N*-methyl-D-aspartate antagonists (*e.g.*, ketamine, nitrous oxide) and γ-amino butyric acid agonists (*e.g.*, benzodiazepines, barbiturates, propofol, volatile anesthetics) induce apoptotic neurodegeneration in the neonatal rodent brain with subsequent neurocognitive impairment.[2–14] Thus, virtually all general anesthetic agents used in clinical practice are implicated. In rodents, the most prominent effects have been observed at postnatal day 7, which is also the peak period for synaptogenesis. Recently, similar injuries have been observed in the monkey brain when exposed to the *N*-methyl-D-aspartate antagonist ketamine.[15,16] These studies have received considerable attention in the pediatric anesthetic community and in the media. However, the applicability of these animal data to humans undergoing anesthesia in early life remains uncertain.

There are many obstacles to studying the possible neurotoxic effects of anesthetics in surgical neonates and infants. In this population, the effects of surgery and pathology cannot easily be distinguished from the effects of anesthesia because children are usually anesthetized for surgical and pathologic reasons. To address this issue scientifically, various methodologies have been proposed.[17–19] Although a randomized controlled trial of regional anesthesia compared with general anesthesia in neonates undergoing inguinal hernia repair is in process,[18] the results of detailed neurobehavioral assessments will not be available for at least 5 yr. Epidemiologic studies are few,[20] but five observational studies have been published recently.[21–25] Overall, these studies have been unable to shed light on the association between anesthesia exposure and subsequent neurocognitive impairment. The studies suffer from small sample sizes, large age ranges with few neonates and infants, and problems with migration, loss to follow-up, and the inclusion of different diseases and surgical procedures.

In this study, therefore, using nationwide population registers, we compared the academic performance of all adolescents born in Denmark from 1986–1990 who had inguinal hernia repair during the first year of life with a randomly selected 5% population sample of age-matched cohorts. The strengths of our study compared with those of previous investigations are its sample size—which includes the unselected (nationwide) nature of the sample and the ability to adjust for confounding factors—and a clinically relevant outcome.

Materials and Methods

This study is based on the Danish Civil Registration System,[26] which identifies individuals using unique personal identification numbers that can be linked through Statistics Denmark (Copenhagen, Denmark) to several thematically organized databases (registers). Information from four registers was included in the present study: the Danish Demographic Database (Dansk Demografisk Database), which includes information on parental identity, birth and death dates, migration, and location[27]; the Danish National Hospital Register, which includes information on overnight hospital stays and operations as well as outpatient procedures for nonpsychiatric illnesses[28]; the Integrated Database for Labour Market Research, which contains annual information on education and employment status; and the Register of Compulsory School Completion Assessments and Test Scores compiled by the Danish Ministry of Education from school reports.[29]

Included in the study was the cohort born from 1986 to 1990. The exposure group consisted of all individuals that underwent surgery for hernia before age 1 yr as identified using codes from the International Classification of Diseases, Eighth Revision (*i.e.*, 406, 407, 408, 409). The comparison group consisted of a randomly selected 5% population sample within this cohort. This control group was selected by randomly choosing 5% of the days in a year (18 dates). Then, for each birth year included, data from all individuals born on these dates were extracted from the Danish Civil Registration System.

Overlaps between the two groups were allocated to the exposure group. Individuals in either study group who died or migrated before June 1, 2006, were excluded from the investigation.

The outcome was ninth grade test average and average teacher rating. All Danish students in ninth grade (aged 15 or 16 y) are required to complete a standardized, nationwide general test of academic achievement, which is scored on a scale of 0–13. Average performance is rated as 8; higher scores correspond with better performance. Tests cover major domains of academic achievement, including Danish and foreign languages, mathematics, hard science, and social science. Test scores were supplemented by teacher ratings of student performance in a given subject during the academic year. Within this birth cohort, information on teacher scores was available for the years 2002 to 2006. Average test scores and average teacher scores were analyzed. Using the available data, an average score was calculated for each student.

Individuals for whom either a test score or teacher score was unavailable on any subject composed a nonattainment group. Although "nonattainment" most often denotes children with special needs that prohibit them from following the standard ninth grade course curriculum (*i.e.*, neuropsychological or severe functional limitations), the group also includes dropouts and children who elect to go to "alternative" schools that do not use standardized testing (*e.g.*, Rudolf Steiner schools). Test score nonattainment, therefore, is unusual, as reflected by the fact that, in the general population, 87% of children obtained ninth grade test scores.

As a test of the validity of test score nonattainment as an indicator of developmental problems, we did a preliminary outcomes analysis of children who underwent neurosurgical procedures within the first year of life. It is noteworthy that, among this group of individuals, approximately half subsequently completed ninth grade and had test scores. Moreover, the scores obtained by this cohort were significantly

lower on average when compared with the control group, demonstrating the validity of our data.

Multiple potential confounding factors were identified in a previous study[30] of academic performance comparing twins *versus* singletons, including sex, birth weight, and paternal and maternal age and education. Therefore, we categorized birth weight in intervals: up to 1,499, 1,500–1,999, 2,000–2,499, 2,500–2,999, 3,000–3,999, and 4,000 g or more. Likewise, variables were determined for paternal (*i.e.*, up to 22, 22–30, 30–40, and 40 yr or older) and maternal (*i.e.*, up to 20, 20–28, 28–36, and 36 yr or older) age. Educational attainments were coded as categorical variables for the highest obtained education by October 1, 2005. By that date, paternal age ranged between 32 and 64 yr (median 47 yr) and maternal age ranged between 31 and 63 yr (median 45 yr). Variables were coded with values from 0 to 6, corresponding to the following categories: primary school, vocational school, secondary education, short higher education, medium higher education, bachelor's degree, and master's degree or doctorate. In regression analysis, "short higher education," "medium higher education," and bachelor's degree were combined into a single category (*i.e.*, "short higher education"). The percentage of individuals in the hernia group for each of the five birth years represented by the population cohort were very similar; as listed sequentially from 1986 to 1990, these proportions were 16.2, 16.4, 17.4, 14.1, and 15.7%, respectively.

Statistical Analysis

Analysis of differences in average test and teacher scores between the exposure and control groups was done using a linear regression model that adjusted for other covariates. Model assumptions were checked by residual plots and quantale plots of residuals. Analysis of the difference in risk of not obtaining test or teacher scores was performed using a logistic regression model that adjusted for the same covariates used in analysis of average scores. Statistical significance was determined at a 5% significance level and 95% CIs were used. All analyses were performed using STATA (version 10.0; STATA Corp., College Station, TX).

To investigate whether, as a result of the observational nature of this study, there could be residual bias in the estimated differences in average test scores and risk of test score nonattainment between anesthetic-exposed children and children in the control group, we performed a propensity score analysis (PSA) that allowed us to make further adjustments for potential confounding factors.[31]

We estimated propensity scores for the assignment to treatment using logistic regression analysis, incorporating the same covariates used in regression analysis: sex, birth weight, and paternal and maternal age and educational level. Three additional covariates were incorporated to predict propensity scores: weeks' gestational age, birth weight (continuous variable), and congenital malformations. Weeks' gestational age is highly correlated with birth weight and hence vulnerable to colinearity problems in traditional regression analysis. To make more careful adjustments for birth weight, we included a second-order interaction term between sex—birth weight as a categorical variable and birth weight as a continuous variable—corresponding to separate regression lines of risk of hernia on birth weight within each category of sex and each category of birth weight. Moreover, we included four first-order interaction terms between sex and each of the following variables: weeks' gestational age (continuous), congenital malformations, and paternal and maternal education levels. Finally, we included the same variables on paternal and maternal age as were included in regression analysis without propensity scores (non-PSA).

We then performed a stratified PSA where we defined five strata in our analysis sample based on propensity score quintiles.[32] In linear regression analysis of average test scores and logistic regression analysis of the risk of test score nonattainment, this procedure was done by including the quintile-grouped propensity score variable as a factor variable in the regression model. We also included the variables already used in the non-PSA. We chose the stratified PSA among different propensity score methods because the use of the quintiles rather than the actual propensity scores gave some robustness toward the risk of having extreme values of the propensity scores with too high influence on the estimation. However, for completeness, we performed a supplementary number of different PSA based more on the exact value of the propensity score estimate. Specifically, we carried out five alternative PSAs. The first, regression (covariance) adjusted PSA, was done by including the propensity score as a continuous covariate in each of the regression analyses together with the other variables from the non-PSA.[32] The next three PSA analyses were all weighted analyses using different functions of the propensity scores as weights.[33] The first used the inverse of the propensity score as weight (inverse probability-to-treatment weight) and estimates the response difference in a population with the same distribution of propensity score covariates as in the study population. The second used the weight 1 in the exposure group and weight equal to the estimated conditional treatment odds in the control group, estimating the response difference in a population with the same distribution of propensity score covariates as the one observed in the treated population. The third analysis used weight 1 in the control group and weight equal to the conditional control group odds in the treatment group, estimating the response difference in a population with the same distribution of propensity score covariates as the one observed in the untreated population. As a final analysis, we made a matched analysis where each exposure group child was matched to a control group child using, as matching criteria, the individual nearest to the exposure group child using the Mahalanobis metric as distance and restricting potential candidates for the match to include those within a preset amount (caliper) of the exposure group child's estimated propensity score, or rather, the logit of the propensity

score.[31,32,34] The Mahalanobis distance was calculated using the following variables, as also used in the non-PSA: sex, birth weight (categorical), and paternal and maternal age and education. As a result of the large size of control group, we used the rather small caliper of one sixty-fourth SD of the logit of the propensity score for the greater part of the matching.

Among exposure group children for whom no control match was available within these narrow bounds, we increased the caliper sufficiently to include candidates among whom a match could be made. The largest caliper necessary for this procedure was just below three SDs (11/4 × SD). When matching was complete, we compared average grades using a paired Student *t* test. Risk of test score nonattainment was compared using conditional logistic regression.

As a means of understanding if weighted analysis was influenced by very large or small estimated propensity scores for some individuals, we performed the three weighted analyses on the subsample. Analysis was restricted to individuals with propensity scores among the 99% most central of the estimated values.

Results

Between 1986 and 1990 in Denmark, a total of 2,689 individuals underwent surgery for hernia during their first year of life. The control group consisted of an age-matched cohort of 14,575 individuals. The proportion of children who died before age 1 yr was smaller in the exposure group compared with that in the control group (0.22 *vs.* 0.75%). This result was anticipated because anesthetic-exposed children were selected conditional on survival until hernia operation. Taking the time under risk of death into account, the mortality rate per 100,000 person-years between age 1 month and 1 yr was 2.94 for anesthetic-exposed children and 1.52 within the control group. The mortality rate was standardized to correspond to a constant population size during 11 months. The mortality rate after age 1 yr, conditional on survival to that age, was 1.04% for anesthetic-exposed children and 0.50% for the control group. Migration rates (before June 1, 2006) were slightly lower in the exposure group than in the control group (4.1 *vs.* 5.2%). Therefore, the study base for all subsequent analyses consisted of 2,547 (94.7%) individuals from the exposure group and 13,640 (93.6%) from the control group.

The distribution of several of the confounders in the exposure group was quite different from that in control group. Boys constituted 89.0% of the exposure group compared with 51.0% in the control group. Mean birth weight was 3,000 g for the exposure group and 3,437 g for the control group. Paternal and maternal age were quite similar between the two study groups: 30.3 *versus* 30.7 yr for paternal and 27.8 *versus* 28.1 yr for maternal age, respectively. Finally, the parents of children in the exposure group had less education than parents of children in the control group. Mean education scores (where higher scores correspond with more education) of fathers were 1.49 *versus* 1.68, respectively; for mothers, these scores were 1.53 *versus* 1.77 (table 1).

Table 1. Characteristics of Early Anesthetic Exposure *versus* Control Group: Denmark, 1986–1990 Birth Cohort

Characteristic	Exposure Group (n = 2,689)	Control Group (n = 14,575)
Death	34 (1.3)	183 (1.3)
1–365 d after birth	6 (0.2)	109 (0.7)
>365 d after birth	28 (1.0)	74 (0.5)
Migration	109 (4.1)	752 (5.2)
Study base	2,547 (94.7)	13,640 (93.6)
Congenital malformation	316 (12.4)	624 (4.6)
Deceased	8 (23.5)	39 (21.3)
Migrant	9 (8.3)	33 (4.4)
Birth weight	2,541 (99.8)	13,616 (99.8)
<1,500 g	152 (6.0)	70 (0.5)
Birth weight, g	3,000 ± 798	3,437 ± 556
≤1,499	25 (16.4)	11 (15.7)
≥1,500	291 (12.2)	610 (4.5)
Sex (boy)	2,266 (89.0)	6,955 (51.0)
Paternal age, yr	30.3 ± 5.4	30.7 ± 5.4
Maternal age, yr	27.8 ± 4.9	28.1 ± 4.8
Paternal education	1.49 ± 1.71	1.68 ± 1.78
Maternal education	1.53 ± 1.66	1.77 ± 1.74
Average test score	7.73 ± 1.09	7.99 ± 1.08
Boy	7.68 ± 1.08	7.83 ± 1.08
Girl	8.08 ± 1.06	8.14 ± 1.06
Average teacher score	7.71 ± 1.11	8.03 ± 1.09
Boy	7.65 ± 1.11	7.80 ± 1.10
Girl	8.20 ± 1.01	8.25 ± 1.04
Test score	2,016 (79.2)	11,850 (86.9)
Boy	1,771 (78.2)	5,843 (84.0)
Girl	245 (87.2)	6,007 (89.9)
Teacher score	2,028 (79.6)	11,893 (87.2)
Boy	1,782 (78.6)	5,876 (84.5)
Girl	246 (87.5)	6,017 (90.0)

All data are presented as No. (%) or mean ± SD unless otherwise specified.

The distribution of average test scores in the exposure *versus* control group is shown in figure 1. SDs in both groups were approximately 1, making the difference in scores readily interpretable. The figure shows better academic performance in the control *versus* exposure group. The average (SD) test score in the exposure group was 7.73 (1.09) compared with 7.99 (1.08) in the control group, resulting in a mean difference of 0.26 (95% CI, 0.21–0.31) and corresponding to approximately one quarter of an SD. Restricting the comparison to individuals of the same sex, the difference was less pronounced. The average test scores for boys was 7.68 *versus* 7.83, respectively, corresponding to a difference of 0.15 (95% CI, 0.10–0.21). Among girls, average test scores were 8.08 *versus* 8.14, respectively, corresponding to a difference of 0.06 (95% CI, −0.08 to 0.19).

A similar difference between the exposure *versus* control group among individuals of the same sex was seen when looking at average teacher scores. The average teacher score

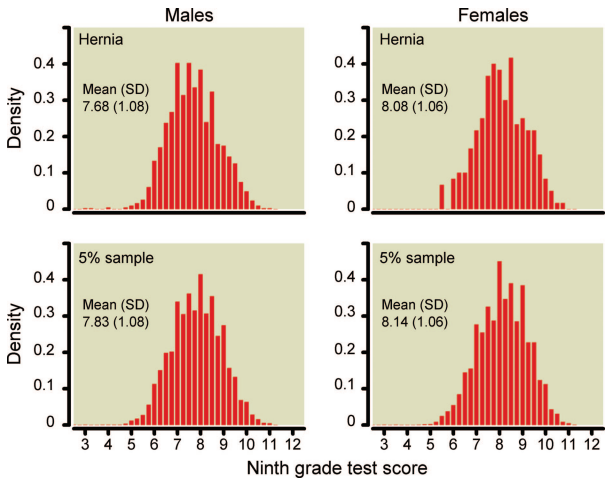

Fig. 1. Distribution of ninth grade mean test scores for Danish adolescents (born 1986–1990) who underwent inguinal hernia repair in infancy (n = 2,547) *versus* a control group composed of a randomly selected 5% population sample of age-matched cohorts (n = 14,575).

for boys was 7.65 *versus* 7.80, respectively, corresponding to a difference of 0.15 (95% CI, 0.09–0.21. Among girls, this score was 8.20 *versus* 8.25, respectively, corresponding to a difference of 0.05 (95% CI, −0.08 to 0.19).

Although the unadjusted comparison of average test scores for exposure *versus* control group children as separated by sex suggests some interaction between sex and exposure, no interaction was found in the adjusted analysis.

Unadjusted differences in average test scores between different groups of confounding variables are shown in table 2. Higher scores were found among girls for higher birth weight, higher paternal and maternal age, and higher paternal and maternal education. In table 3, the results of multivariate analysis of academic performance are shown. Average test scores in the exposure group were not statistically different from those in the control group. The estimated mean in the exposure group was 0.04 below that in the control group (95% CI, −0.01 to 0.09). The pattern of the association between confounders and outcomes in the adjusted analysis was as in the unadjusted table (table 2), but the associations were less pronounced. The results of the adjusted analysis of average teacher scores were similar (data not shown).

The unadjusted risk of not obtaining an average test score was higher in the exposure group than in the control group: 20.8 *versus* 13.1%, corresponding to a risk difference of 7.7% (95% CI, 6.0–9.4%). Approximately 21.8% of boys in the exposure group never attained test scores compared with 16.0% in the control group, corresponding to a difference of 5.8% (95% CI, 3.9–7.8%). Among girls, the corresponding proportion was 12.8% in the exposure group compared with 10.1% in the control group, with a difference of 2.7% (95% CI, 1.3–6.6%). After adjusting for the same variables noted in the adjusted analysis of the average test scores, we found an odds ratio (OR) of 1.18 for not obtaining test scores when comparing the exposure and control groups (95% CI, 1.04–1.35; table 4). These data include children who did not attain a test score as well as with no score recorded.

Table 2. Mean Difference in Average Test Scores: Denmark, 1986–1990 Birth Cohort (n = 13,866)

Characteristic	No.	Contrast (95% CI)
Exposure *vs.* control group (ref. control)	11,850	—
Exposure	2,016	−0.26 (−0.31 to −0.21)
Sex (ref. Boy)	7,614	—
Girl	6,252	0.34 (0.30–0.37)
Birth weight, g (ref. 3,000–3,999 g)	9,057	—
<1,499	148	−0.23 (−0.40 to −0.05)
1,500–1,999	203	−0.23 (−0.38 to −0.08)
2,000–2,499	521	−0.23 (−0.33 to −0.14)
2,500–2,999	1,890	−0.19 (−0.24 to −0.13)
>4,000	2,032	0.06 (0.01–0.12)
Paternal age (ref. 22–30)	6,030	—
≤22	413	−0.55 (−0.65 to −0.44)
30–40	6,355	0.22 (0.18–0.26)
>40	793	0.27 (0.19–0.35)
Maternal age (ref. 20–28)	6,939	—
<20	359	−0.59 (−0.70 to −0.47)
28–36	5,705	0.29 (0.25–0.33)
>36	859	0.42 (0.35–0.50)
Paternal education (ref. basic school)	3,142	—
Vocational	5,691	0.33 (0.28–0.37)
Short	3,098	0.77 (0.72–0.82)
Long	1,088	1.29 (1.22–1.36)
Maternal education (ref. basic school)	3,292	—
Vocational	5,237	0.30 (0.25–0.34)
Short	4,376	0.83 (0.79–0.88)
Long	627	1.39 (1.31–1.48)

Long = master's degree or doctorate; Short = short higher education, medium higher education, bachelor's degree; Vocational = primary school, vocational school, secondary education.

When children with birth weights lower than 1,500 g were excluded from analysis, results remained unchanged. For this group, the difference in test scores is −0.04 (95% CI, −0.09 to 0.02) and there is an OR of 1.19 (95% CI; 1.04–1.36) for test score nonattainment.

In addition, when the Danish National Patient Register was used to exclude from analysis children with other congenital malformations (as diagnosed from birth to 2006 using codes from the International Classification of Diseases, Eighth Revision [*i.e.*, 740.00–759.99], or Tenth Revision [*i.e.*, Q0.0–Q99.9]), test score differences between the exposure and the control group remained nearly unchanged (0.05 *vs.* 0.04; 95% CI, 0.00–0.11; $P = 0.063$). In addition, the increased propor-

Table 3. Regression Analysis of Test Scores: Denmark, 1986–1990 Birth Cohort (n = 12,573)

Characteristic	Contrast (95% CI)
Exposure *vs.* control group (ref. control)	—
Exposure	−0.04 (−0.09 to 0.01)
Sex (ref. Boy)	—
Girl	0.35 (0.32 to 0.39)
Birth weight, g (ref. 3,000–3,999 g)	—
≤1,499	−0.09 (−0.26 to 0.08)
1,500–1,999	−0.07 (−0.21 to 0.08)
2,000–2,499	−0.07 (−0.16 to 0.02)
2,500–2,999	−0.09 (−0.14 to −0.04)
≥4,000	0.05 (0.00 to 0.10)
Paternal age (ref. 22–30)	—
≤22	−0.21 (−0.32 to −0.10)
30–40	0.02 (−0.02 to 0.07)
>40	0.06 (−0.02 to 0.15)
Maternal age (ref. 20–28)	—
<20	−0.30 (−0.42 to −0.17)
28–36	0.07 (0.03 to 0.11)
>36	0.12 (0.03 to 0.20)
Paternal education (ref. basic school)	—
Vocational	0.22 (0.18 to 0.27)
Short	0.52 (0.47 to 0.57)
Long	0.83 (0.75 to 0.90)
Maternal education (ref. basic school)	—
Vocational	0.22 (0.18 to 0.27)
Short	0.56 (0.51 to 0.61)
Long	0.83 (0.74 to 0.93)

Sample size (n = 12,573) for regression analysis corresponds to 90.7% of all graduates.

Long = master's degree or doctorate; Short = short higher education, medium higher education, bachelor's degree; Vocational = primary school, vocational school, secondary education.

Table 4. Logistic Regression of Unavailability of Test Scores on Covariates: Denmark, 1986–1990 Birth Cohort (N = 14,536)

Characteristic	Odds Ratio (95% CI)
Exposure *vs.* control group (ref. control)	—
Exposure	1.18 (1.04–1.35)
Sex (ref. Boy)	—
Girl	0.56 (0.51–0.63)
Birth weight, g (ref. 3,000–3,999 g)	—
≤1,499	2.65 (1.91–3.68)
1,500–1,999	1.96 (1.43–2.67)
2,000–2,499	1.37 (1.09–1.72)
2,500–2,999	1.28 (1.11–1.47)
≥4,000	0.96 (0.82–1.11)
Paternal age (ref. 22–30)	—
≤22	1.25 (0.98–1.60)
30–40	0.84 (0.75–0.95)
>40	1.01 (0.79–1.29)
Maternal age (ref. 20–28)	—
≤20	1.17 (0.90–1.53)
28–36	0.96 (0.85–1.08)
36+	1.02 (0.79–1.31)
Paternal education (ref. basic school)	—
Vocational	0.65 (0.58–0.72)
Short	0.48 (0.41–0.56)
Long	0.41 (0.31–0.55)
Maternal education (ref. basic school)	—
Vocational	0.59 (0.53–0.66)
Short	0.52 (0.46–0.60)
Long	0.48 (0.34–0.69)

Sample size (N = 14,536) for logistic regression analysis corresponds to 89.8% of the sample under study.

Long = master's degree or doctorate; Short = short higher education, medium higher education, bachelor's degree; Vocational = primary school, vocational school, secondary education.

tion of test score nonattainment became nonsignificant (OR = 1.13; 95% CI, 0.98–1.31; $P = 0.085$).

In the exposure group, the frequency of other congenital malformations was higher than in the control group (12.4 *vs.* 4.8%; table 1).

Excluding children with congenital malformations and children with a birth weight lower than 1,500 g together from the analyses yielded similar results as when children with congenital malformations alone were excluded.

The checking of our model assumptions did not find any violations of variance homogeneity, model misspecification, or normality.

PSA gave essentially the same results as corresponding analysis without propensity scores (table 5). The estimated difference between average test scores of children in the exposure group *versus* those in the control group was −0.03 (95% CI, −0.09 to 0.02), which is close to the estimate of −0.04 (95% CI, −0.09 to 0.01) for the analysis without propensity scores. Similarly, the OR for test score nonattainment associated with early anesthetic exposure was estimated to be 1.15 (95% CI, 1.01–1.32), a result that again was comparable with the estimate of 1.18 (95% CI, 1.04–1.35). We also tested for possible interaction between treatment and propensity quintile, but none was found ($P = 0.64$ for average test scores; $P = 0.28$ for test score nonattainment). The results from the different PSAs, seen in table 5, are very similar and do not indicate any substantial bias unaccounted for in the non-PSA.

Point estimates of the difference in average test scores of children in the exposure *versus* control group are very close. Although estimated ORs in risk analysis of test score nonattainment seem to vary a bit more across the different PSAs, they are still all well in agreement with the estimated OR and CI of the non-PSA analyses.

Discussion

In this nationwide follow-up study of birth cohorts from 1986 to 1990 in Denmark, we have shown that children who had operations for inguinal hernia in infancy—and were thus

Table 5. Nonpropensity Score Analysis Response Differences in Early Anesthetic Exposure *versus* Control Group: Denmark, 1986–1990 Birth Cohort

Characteristic	Test Score Average Difference (95% CI)	Test Score Nonattainment Odds Ratio (95% CI)
Non-PSA	−0.04 (−0.09 to 0.01)	1.18 (1.04–1.35)
Stratification on quintiles	−0.05 (−0.10 to 0.01)	1.23 (1.08–1.40)
Stratification on quintiles*	−0.03 (−0.09 to 0.02)	1.16 (1.02–1.33)
Regression (covariance) adjustment	−0.04 (−0.09 to 0.02)	1.14 (1.00–1.31)
Inverse probability to treatment weight†	—	—
Analysis population	−0.02 (−0.11 to 0.06)	1.14 (0.93–1.39)
Anesthetic exposed	−0.06 (−0.11 to 0.00)	1.17 (0.99–1.38)
Control	−0.02 (−0.10 to 0.07)	1.09 (0.89–1.34)
Matched-paired analysis	−0.03 (−0.10 to 0.04)	1.24 (1.06–1.45)

Response of average test score and response of test score nonattainment is considered. In the latter, the response difference is measured by the odds ratio.

* Analysis includes adjustments for sex, birth weight, and paternal and maternal age and education. † Test score differences in the subpopulation defined by being among the 99% with the most central propensity scores were as follows: analysis population, −0.03 (95% CI, −0.12 to 0.05); anesthetic exposed, −0.04 (95% CI, −0.09 to 0.02); control, −0.03 (95% CI, −0.11 to 0.06). Odds ratios in that subpopulation were, respectively, as follows: 1.14 (95% CI, 0.93–1.39, 1.16 (95% CI, 1.00–1.34), and 1.10 (95% CI, 0.90–1.34).

exposed to a single, brief anesthetic procedure in infancy—had academic test scores at age 15 or 16 yr that were nearly 5% of an SD lower than those observed in the background population. Boys had test scores that were on average 34% of an SD lower than girls. The effect of belonging to the exposure group was actually the smallest of all the included variables in the final model (sex, birth weight, and parental age and education). Thus, this study, with a 80% power to detect an academic test difference of 0.08 SD, did not provide evidence for a general neurotoxic effect of general anesthetics in the first year of life, although no evidence for a difference in test scores excludes the possibility of more subtle effects. Furthermore, the 1.18 higher risk of test score nonattainment suggests that a small fraction of children in the exposure group were disadvantaged either from other diseases/conditions or from susceptibility to anesthesia/surgery, potentially on a sex-based or genetic basis. Randomized controlled trials may shed more light on this issue.

When children with other congenital malformations were excluded from analysis, differences in test score between the exposed and control group remained nearly unchanged. In addition, the increased proportion of test score nonattainment was attenuated. The increased number of disadvantaged children in the exposure group is also reflected in the slightly increased mortality seen after age 1 yr. This observation supports the recent findings of DiMaggio *et al.*[23] Their study,[23] which reported on a birth cohort of 383 children, indicated that children younger than 3 yr undergoing hernia repair are more than twice as likely of being subsequently diagnosed with behavioral/developmental disorders (adjusted hazard ratio 2.3; 95% CI, 1.3–4.1).

The great majority of children in our study who subsequently attained test scores in ninth grade (age 15 or 16 yr) did not show any signs of neurologic impairment, as estimated by similar academic performance when compared with a randomly selected control group. This result is in contrast to sex-based differences: boys have higher test score nonattainment and lower test scores compared with girls, while the exposure group has 1.18 (1.13 when other congenital anomaly cases were excluded) higher test score nonattainment but same test score distribution. In our study, higher test scores were found among girls, as were higher birth weight and higher paternal and maternal age and education. Birth weight lower than 1,500 g appeared as a significant risk factor for test score nonattainment with an OR of 2.65 (95% CI, 1.91–3.68).

The strength of our study lies in its unprecedented size. It includes all children born in Denmark from 1986–1990 who had inguinal hernia repair during infancy. It is a register-based study and includes important covariates for most participants. The expected associations with covariates were observed in our sample, suggesting data of high quality. Moreover, our study focuses exclusively on neonates and infants (*i.e.*, populations assumed to be at the greatest risk of neurotoxicity from general anesthesia) and includes only one well-defined surgical procedure.

In Denmark, we have a national healthcare system with no out-of-pocket expenses for any citizens. This means that data for very few patients are missing in studies of this kind. Because Denmark is ethnically homogeneous, these results need to be replicated for other racial and ethnic groups. In addition, studies with more socioeconomically diverse populations are warranted to investigate potential interactions between anesthesia and these potentially confounding factors.

Although the outcome measures we used are relatively recent, we used relatively historical exposure data. Thus, our data are based on anesthetic exposure that occurred approximately 20 yr ago. Our data therefore do not address current use of newer (and possibly safer) anesthetic techniques, nor do they address improvements in multiparameter monitoring (*e.g.*, pulse oximetry, capnography, hemodynamics, end-tidal inhalational anesthetics). We were unable to explicitly

establish type, route, dose, or duration of the anesthetics administered during surgery. However, during 1986–1990, the vast majority of infants undergoing inguinal hernia repair in Denmark received a general anesthetic technique with halothane or isoflurane with nitrous oxide in oxygen with surgery duration of 30–60 min.[35]

Our study is based on data from the Danish National Patient Register, which include information on all patients admitted to hospitals. The quality of these data has proven acceptable for use with codes from the International Classification of Diseases, Eighth Revision, particularly for surgery and pediatrics, with the highest level of agreement found for congenital malformations.[36]

Our outcome measure, academic performance in adolescence, has a number of advantages. It is normally distributed at a SD of approximately 1 and sensitive, as seen by its association with a series of covariates that we had information on in this study (*i.e.*, sex, birth weight, parental age and education). Animal data are, for the most part, confined to pathologic effects, with only a few studies demonstrating negative effects on behavior and learning. It is noteworthy that several recent animal studies have either observed no negative effects of a single neonatal exposure on subsequent behavior and learning[37–39] or only very subtle effects.[40] In one notable recent exception,[41] repeated exposure to isoflurane in young, but not adult, rodents induced persistent progressive memory impairment, loss of neural stem cells, and reduced neurogenesis.

Translating the ability of rodents to negotiate a water or radial arm maze into a human behavioral correlate is obviously difficult.[42–44] Detailed neurocognitive testing is feasible in smaller, but not in larger, epidemiologic studies. Academic achievement tests were the endpoint in our study rather than intelligence quotient testing. Naglieri *et al.*[45] found that the correlation between intelligence quotient and standardized achievement tests is quite high, averaging 0.70–0.74. The high correlation between the two types of assessments suggests that they would produce similar results. In any case, assessments of academic achievement have a pragmatic advantage over intelligent quotient testing because parents are likely to be more interested in how their child will do in school rather than how they will do in a test of intelligence.

Our results are reassuring in relation to relative short-term exposure to general anesthetics during infancy. However, many questions still remain regarding the use of specific anesthetic drugs (including opioids[46]) and techniques, doses, exposure duration, and relevant outcomes.

In 2008, Loepke *et al.*[42] reviewed the evidence linking exposure to anesthetics and neurocognitive function in children and concluded that "anecdotal data point toward the possibility for neurologic impairment after neonatal surgery and anesthesia." Five cohort studies[21–25] have been published since we conducted this review. In a historical cohort study (n = 593), Wilder *et al.*[21] probed medical records identifying all types of surgeries performed in children before the age of 4 yr. That study[21] indicated an association between having two or more anesthetics and increased risk of learning disabilities. However, these results may be explained by confounders because children with more significant illnesses and comorbidities are more likely to need surgery.

Kalkman *et al.*[22] attempted to estimate neurobehavioral development in children who had been exposed to anesthesia for urological procedures at age 0–6 yr. However, the sample size (n = 243) was unable to demonstrate an association between anesthesia and outcomes. Similarly, in a recent twin study, Bartels *et al.*[25] were unable to demonstrate an association between exposure to anesthesia before the age 3 yr and educational achievement and cognitive problems at age 12 yr, as evidenced by similar learning-related outcomes in monozygotic twins with or without surgery. Again, however, the sample size (n = 110, less than age 3 yr; n = 225, less than age 12 yr) was unable to indicate an association between anesthesia and outcomes.[25]

Sprung *et al.*[24] investigated the effect of obstetric anesthesia on learning disabilities in children aged 5 yr and younger. No evidence could be found for a difference in risk of learning disabilities between children delivered by cesarean section under general anesthesia compared with vaginal delivery. However, quite unexpectedly, they found that children delivered by cesarean section with regional anesthesia had a lower risk of learning disabilities compared with both vaginal delivery and cesarean section under general anesthesia.[24]

General problems with many of the cohort studies published so far is that they include many types of surgeries, the ages of the child at anesthesia exposure usually extend well beyond infancy, and only a small proportion of neonates and infants are included. Anesthetic drugs are some of the most potent and fastest acting drugs available in clinical medicine. The speed of onset of most drugs is limited only by the body's ability to deliver them to their targets, leading to almost immediate profound changes in fundamental physiologic parameters. It is generally assumed that the effects dissipate almost as quickly as they arise and without long-term sequella. The complexity of the human central nervous system complicates the extrapolation of data derived from experimental species to humans. Widespread apoptotic cell death is not uncommon in developing human or rodent brains, but it is a rather integral part of normal brain development.[42–44] Apoptosis can be triggered by physiologic and pathologic stimuli. The number of supernumerary neurons removed by physiologic apoptosis during normal brain development has been widely estimated in humans and rodents to be 50–70% of the entire neuronal cell population.[47] Hence, it is logical to expect significant recovery of function because the pathologic process occurs at a time of great neuroplasticity. Unfortunately, this may not always be the case. Alternatively, withholding anesthetics during painful procedures does not solve this conundrum and is clearly unethical. Structural brain abnormalities and long-term behavioral abnormalities have been extensively documented after painful stimulation in un-

anesthetized newborn humans and animals.[44,48–52] Many different approaches with complementary study designs will be required to accumulate sufficient knowledge that will allow us to conclude whether general anesthesia produces clinically significant neurotoxicity in neonates, infants, and young children.[17–19]

In the ethnically and socioeconomically homogeneous population of Denmark, we found no evidence that a single, relatively brief anesthetic exposure in connection with hernia repair in infancy reduced academic performances at age 15 or 16 yr compared with a control group that consisted of a 5% population sample of randomly selected age-matched cohorts. This finding does not provide any human evidence for a general neurotoxic effect of general anesthetics as reported in animal studies. Nonetheless, higher test score nonattainment rate in this population could suggest that a subgroup of children with early anesthetic exposure are developmentally disadvantaged compared with the background population. However, we assessed only one coarse score of neurobehavioral outcome (academic performance at age 15 or 16 yr). Although our results are reassuring, they cannot exclude effects in more particular domains of neurobehavioral outcome.

References

1. Sims C, Stanley B, Milnes E: The frequency of and indications for general anaesthesia in children in Western Australia 2002–2003. Anaesth Intens Care 2005; 33:623–8
2. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, Tenkova TI, Stefovska V, Turski L, Olney JW: Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 1999; 283:70–4
3. Ikonomidou C, Bittigau P, Ishimaru M, Wozniak DF, Koch C, Genz K, Price MT, Stefovska V, Hörster F, Tenkova T, Dikranian K, Olney JW: Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science 2000; 297: 1056–60
4. 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
5. Ikonomidou C, Bittigau P, Koch C, Genz K, Hoerster F, Felderhoff-Mueser U, Tenkova T, Dikranian K, Olney JW: Neurotransmitters and apoptosis in the developing brain. Biochem Pharmacol 2001; 62:401–5
6. Olney JW, Wozniak DF, Jevtovic-Todorovic V, Farber NB, Bittigau P, Ikonomidou C: Drug-induced apoptotic neurodegeneration in the developing brain. Brain Pathol 2002; 12: 488–98
7. Bittigau P, Sifringer M, Genz K, Reith E, Pospischil D, Govindarajalu S, Dzietko M, Pesditschek S, Mai I, Dikranian K, Olney JW, Ikonomidou C: Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci USA 2002; 99:15089–94
8. Jevtovic-Todorovic V, Wozniak DF, Benshoff ND, Olney JW: A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. Brain Res 2001; 895:264–7
9. Satomoto M, Satoh Y, Terui K, Miyao H, Takishima K, Ito M, Imaki J: Neonatal exposure to sevoflurane induces abnormal social behaviors and deficits in fear conditioning in mice. Anesthesiology 2009; 110:628–37
10. 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
11. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, Olney JW: Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. Br J Pharmacol 2005; 146:189–97
12. Fredriksson A, Pontén E, Gordh T, Eriksson P: Neonatal exposure to a combination of *N*-methyl-D-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology 2007; 107:427–36
13. Sanders RD, Xu J, Shu Y, Fidalgo A, Ma D, Maze M: General anesthetics induce apoptotic neurodegeneration in the neonatal rat spinal cord. Anesth Analg 2008; 106:1708–11
14. Bercker S, Bert B, Bittigau P, Felderhoff-Müser U, Bührer C, Ikonomidou C, Weise M, Kaisers UX, Kerner T: Neurodegeneration in newborn rats following propofol and sevoflurane anesthesia. Neurotox Res 2009; 16:140–7
15. Slikker W Jr, Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, Doerge DR, Scallet AC, Patterson TA, Hanig JP, Paule MG, Wang C: Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci 2007; 98:145–58
16. 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
17. Sun LS, Li G, Dimaggio C, Byrne M, Rauh V, Brooks-Gunn J, Kakavouli A, Wood A; Coinvestigators of the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) Research Network: Anesthesia and neurodevelopment in children: Time for an answer? Anesthesiology 2008;109:757–61
18. Davidson AJ, McCann ME, Morton NS, Myles PS: Anesthesia and outcome after neonatal surgery: The role for randomized trials. Anesthesiology 2008; 109:941–4
19. Hansen TG; Danish Registry Study Group, Flick R, Mayo Clinic Pediatric Anesthesia and Learning Disabilities Study Group. Anesthetic effects on the developing brain: Insights from epidemiology. Anesthesiology 2009; 110:1–3
20. 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
21. 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
22. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, de Jong TP: Behavior and development in children and age at the time of first anesthetic exposure. Anesthesiology 2009; 110:805–12
23. 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
24. 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
25. 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
26. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB: The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006; 53:441–9
27. Petersen JK: The Danish demographic database: Longitudinal data for advanced demographic methods, Research Report

15. Odense, Denmark, Danish Center for Demographic Research, University of Southern Denmark, 2000
28. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH: The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46:263–8
29. Test Assessment and Teaching: An overall evaluation of compulsory school completion assessment and test scores May-June 2004. Copenhagen, Danish Ministry of Education Copenhagen, 2004
30. Christensen K, Petersen I, Skytthe A, Herskind AM, McGue M, Bingley P: Comparison of academic performance of twins and singletons in adolescence: Follow-up study. BMJ 2006; 333:1095–7
31. Rosenbaum PR, Rubin DB: The central role of the propensity score in observational studies for causal effects. Biometrika 1983; 70:41–55
32. D'Agostino RB Jr.: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998; 17:2265–81
33. Sato T, Matsuyama Y: Marginal structural models as a tool for standardization. Epidemiology 2003; 14:680–6
34. Rosenbaum PR, Rubin DB: Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984; 79:516–24
35. Valentin N: Anesthesia for children, Anesthesia, 1st Edition. Edited by Jacobsen E, Andersen TV. Copenhagen, FadL's Forlag, 1991, pp 178–88
36. Mosbech J, Jørgensen J, Madsen M; Rostgaard K, Thornberg K, Poulsen TD: [The national patient registry. Evaluation of data quality]. Ugeskr Laeger 1995; 157:3741–5
37. Loepke AW, Istaphanous GK, McAuliffe JJ 3rd, Miles L, Hughes EA, McCann JC, Harlow KE, Kurth CD, Williams MT, Vorhees CV, Danzer SC: The effects of neonatal isoflurane exposure in mice on brain cell viability, adult behavior, learning, and memory. Anesth Analg 2009; 108:90–104
38. Xu H, Liu ZQ, Liu Y, Zhang WS, Xu B, Xiong YC, Deng XM: Administration of midazolam in infancy does not affect learning and memory of adult mice. Clin Exp Pharmacol Physiol 2009; 36:1144–8
39. Liang G, Ward C, Peng J, Zhao Y, Huang B, Wei H: Isoflurane causes greater neurodegeneration than an equivalent exposure of sevoflurane in the developing brain of neonatal mice. ANESTHESIOLOGY 2010; 112:1325–34
40. Stratmann G, Sall JW, May LD, Bell JS, Magnusson KR, Rau V, Visrodia KH, Alvi RS, Ku B, Lee MT, Dai R: Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 7-day-old rats. ANESTHESIOLOGY 2009; 110:834–48
41. Zhu C, Gao J, Karlsson N, Li Q, Zhang Y, Huang Z, Li H, Kuhn HG, Blomgren K: Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult, rodents. J Cereb Blood Flow Metab 2010; 30:1017–30
42. 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
43. Patel P, Sun L: Update on neonatal anesthetic neurotoxicity: Insight into molecular mechanisms and relevance to humans. ANESTHESIOLOGY 2009; 110:703–8
44. Sanders RD, Ma D, Brooks P, Maze M: Balancing paediatric anaesthesia: Preclinical insights into analgesia, hypnosis, neuroprotection, and neurotoxicity. Br J Anaesth 2008; 101: 597–609
45. Naglieri JA, Bornstein BT: Intelligence and achievement: Just how correlated are they? J Psychoeduc Assess 2003; 21: 244–60
46. Marsh DF, Hatch DJ, Fitzgerald M: Opioid systems and the newborn. Br J Anaesth 1997; 79:787–95
47. Blomgren K, Leist M, Groc L: Pathological apoptosis in the developing brain. Apoptosis 2007; 12:993–1010
48. Anand KJ, Sippell WG, Aynsley-Green A: Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: Effects on the stress response. Lancet 1987; 1:62–6
49. Fitzgerald M: The development of nociceptive circuits. Nat Rev Neurosci 2005; 6:507–20
50. Taddio A, Katz J, Ilersich AL, Koren G: Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet 1997; 349:599–603
51. Hermann C, Hohmeister J, Demirakça S, Zohsel K, Flor H: Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain 2006; 125:278–85
52. Page GG, Blakely WP, Kim M: The impact of early repeated pain experiences on stress responsiveness and emotionality at maturity in rats. Brain Behav Immun 2005; 19:78–87