ANESTHESIA AND THE NEWBORN BRAIN

Capitol Anesthesiology Association
Dell Children’s Medical Center

Carlos-Nicholas Lee, M.D.
“Children who received general anesthesia repeatedly before the age of 2 had a doubling of their risk for learning disabilities at school age.”

“...a debate has intensified about the link between anesthetics and learning disabilities. Many animal studies have shown that the drugs hamper brain development.”

“One possibility is that exposure to these classes of drugs—known as NMDA antagonists or GABA agonists—during periods of rapid brain growth affects the brain's normal process...”
Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys

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Abstract

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Anesthesia: Is it Safe for Young Brains?

When infants or young children need surgery, does anesthesia affect their developing brains?

With more than 1 million children under age 4 requiring anesthesia for surgery in the United States each year, the Food and Drug Administration (FDA) and other health organizations are working together to answer this question.

Previous scientific studies in young animals have shown that commonly used anesthetics can be harmful to the developing brain. However, results have been mixed in children. Some studies of infants and young children undergoing anesthesia have reported long-term deficits in learning and behavior; other studies have not.

These conflicting results show that more research is needed to fully understand the risks anesthesia may pose to very young patients.

To close these research gaps, FDA and the International Anesthesia Research Society (IARS) started an initiative called SmartTots (Strategies for Mitigating Anesthesia-Related Neurotoxicity in Tots). SmartTots seeks to ensure that children under age 4 will be as safe as possible when they need anesthesia during surgery.

Studies have shown that this is a period of significant brain development in young children.

“Our hope is that research funded through SmartTots will help us design the safest anesthetic regimens possible,” says Bob Engberg, M.D., director of the Division of Anesthesia, Analgesia and Addiction Products at FDA. “This research can potentially focus the development of new and safer anesthetic drugs for use in pediatric medicine.”

According to SmartTots steering committee co-chair James Ramsey, M.D., young children usually do not undergo surgery unless the procedure is vital to their health. “Therefore, postponing a necessary procedure may itself lead to significant health problems and may not be an option for the majority of children,” Ramsey says.

Ongoing Research

SmartTots was launched in 2010 in part to fund research that would build on the work done at FDA and several universities.

Since 2003, Mindy Pauley, Ph.D., director of the Division of Neurotoxicology at FDA’s National Center for...
CONSENSUS STATEMENT ON THE USE OF ANESTHETICS AND SEDATIVES IN CHILDREN
December 2012

Each year, millions of young children require surgery and other procedures for serious or life-threatening medical conditions or to improve their quality of life. Anesthetic and sedative drugs are widely used to help ensure the safety, health, and comfort of children undergoing these procedures. However, increasing evidence from research studies suggests the benefits of these agents should be considered in the context of their potential to cause harmful effects.

Previous research in young animals and children has raised concerns that exposure to commonly used anesthetics may produce adverse neurobehavioral effects. However, 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 pre-existing conditions. Furthermore, the findings in children have been mixed, with some studies of infants and young children undergoing anesthesia or sedation finding long-term deficits in learning and behavior while others have not.

Clearly, additional research is urgently needed to identify any possible risks to young children. In the absence of conclusive evidence, it would be unethical to withhold sedation and anesthesia when necessary. Instead, health care providers should do the following:

- Discuss with parents and other caretakers the risks and benefits of procedures requiring anesthetics or sedatives, as well as the known health risks of not treating certain conditions
- Stay informed of new developments in this area
- Recognize that current anesthetics and sedatives are necessary for infants and children who require surgery or other painful and stressful procedures

Endorsed by:

1. IARS
2. American Academy of Pediatrics
3. FDA
4. Society for Pediatric Anesthesia
5. European Society of Anesthesiology
• Propofol in subclinical doses in neonatal mice demonstrated long-term functional impairments. This dosing was around one-fourth the dose needed for surgical anesthesia.

• Exposure to isoflurane revealed neuroapoptosis which were potentiated by nitrous oxide and midazolam.

• Sevoflurane at sub-anesthetic concentrations resulted in increased neuroapoptosis, abnormal social and learning behaviors.

• A weight based ketamine dose to baby rats demonstrated neurotoxicity and impaired learning into adulthood whereas the same dose in juvenile rats do not.
Physiological Disturbance May Contribute to Neurodegeneration Induced by Isoflurane or Sevoflurane in 14 Day Old Rats

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Abstract

Background: Volatile anesthetics are widely used in pediatric anesthesia but their potential neurotoxicity raise significant concerns regarding sequelae after anesthesia. However, whether physiological disturbance during anesthetic exposure contributes to such side effects remains unknown. The aim of the current study is to compare the neurotoxic effects of isoflurane and sevoflurane in 14 day old rat pups under spontaneous breathing or ventilated conditions.

Methods: Postnatal 14 day rats were assigned to one of five groups: 1) spontaneous breathing (SB) + room air (control, n = 17); 2) SB + isoflurane (n = 35); 3) SB + sevoflurane (n = 37); 4) mechanical ventilation (MV) + iso-flurane (n = 29); 5) MV + sevoflurane (n = 33). Anesthetized animal received either 1.7% isoflurane or 2.4% sevoflurane for 4 hours. Arterial blood gases and blood pressure were monitored in the anesthetized groups. Neurodegeneration in the CA3 region of hippocampus was assessed with terminal deoxynucleotidyl transferase-mediated DNA nick-end labeling immediately after exposure. Spatial learning and memory were evaluated with the Morris water maze in other cohorts 14 days after experiments.

Results: Most rats in the SB groups developed physiological disturbance whereas ventilated rats did not but become hyperglycemic. Mortality from anesthesia in the SB groups was significantly higher than that in the MV groups. Cell death in the SB but not MV groups was significantly higher than controls. SB + anesthesia groups performed worse on the Morris water maze behavioral test, but no deficits were found in the MV group compared with the controls.

Conclusions: These findings could suggest that physiological disturbance induced by isoflurane or sevoflurane anesthesia may also contribute to their neurotoxicity.


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Introduction

Volatile anesthetics such as isoflurane [1] and sevoflurane [2] likely act on gamma aminobutyric acid (GABA_A) receptors that have been demonstrated to be neurotoxic in the developing brain. Brain growth rate is highest during the first 2 postnatal weeks in rodents [3,4]. Previous studies indicated long-term exposure to volatile anesthetics during this period cause neuronal death in the hippocampus and subsequently lead to cognitive dysfunction [5], although other studies have reported conflicting results [6,7]. These findings raise concerns regarding the long-lasting neuro–logical sequelae of anesthesia-exposure during early childhood. Many studies, however, were carried out without airway management, animals were placed in an anesthetic chamber flushed continuously with volatile anesthetics mixed in air and pure oxygen, in which mortality reached up to 20–30% and blood gases were often beyond the physiological ranges.

Animal Model Limitations

metabolic acidosis [8–10]. However, whether those physiological disturbance caused by anesthetic induced states contributes to the neurotoxicity is open a question. Herein we report a comparison study to determine whether there were the different changes of physiological parameters, mortality, neurotoxicity and cognitive function when postnatal 14 day rats were anesthetized with isoflurane or sevoflurane for 4 hours under either spontaneous breathing or mechanical ventilation.

Methods

Ethics Statement and Animals

All experiments were approved by the Animal Care and Use Committee of Wenzhou Medical University without a number (Wenzhou, China), and all surgery was performed under anesthesia, and all efforts were made to minimize animal use including that the sample size was calculated with 90% power at a
Mouse Facts

- The average weight of an adult mouse is 20 g
- The heart rate of an adult mouse is around 600 bpm, whereas a neonatal mice is around 280 bpm
- The respiratory rate of a mouse is around 163 times per minute
Delayed Environmental Enrichment Reverses Sevoflurane-induced Memory Impairment in Rats


ABSTRACT

Background: Anesthesia given to immature rodents causes cognitive decline, raising the possibility that the same might be true for millions of children undergoing surgical procedures under general anesthesia each year. We tested the hypothesis that anesthesia-induced cognitive decline in rats is treatable. We also tested if anesthesia-induced cognitive decline is aggravated by tissue injury.

Methods: Seven-day old rats underwent sevoflurane anesthesia (1 minimum alveolar concentration, 4 h) with or without tail clamping. At 4 weeks, rats were randomized to environmental enrichment or normal housing. At 6 weeks rats underwent neurocognitive testing, which consisted of fear conditioning, spatial reference memory, and water maze-based memory consolidation tests, and interrogated working memory, short-term memory, and early long-term memory.

Results: Sevoflurane treated rats had a greater escape latency when the delay between memory acquisition and memory retrieval was increased from 1 min to 1 h, indicating that short-term memory was impaired. Environmental enrichment reversed the effects of sevoflurane on short-term memory and generally improved many tested aspects of cognitive function, both in sevoflurane-treated and control animals. The performance of tail-clamped rats did not differ from those rats receiving anesthesia alone.

Conclusion: Sevoflurane-induced cognitive decline in rats is treatable. Delayed environmental enrichment reversed the sevoflurane-induced impairment in short-term memory. Tissue injury did not worsen the anesthesia-induced memory impairment. These findings may have relevance to neonatal and pediatric anesthesia.

What We Already Know about This Topic

- Potent volatile anesthetic agents produce long-term neurocognitive impairment in developing rodents
- Sevoflurane is the preferred volatile agent in pediatric anesthesia
- Environmental enrichment improves brain function

What This Article Tells Us That Is New

- Sevoflurane, with or without tissue injury, causes long-term impairment in spatial short-term memory in infantile rats that is unaffected by tissue injury
- Delayed environmental enrichment treats this long-term neurocognitive impairment

Sevoflurane, given as a single anesthetic agent, causes neurodegeneration in the infantile rodent brain14-15 long-term neurocognitive deficits later in life.14-15 (but also see9). Sevoflurane is now more commonly used in pediatric anesthesia and its neurotoxicity profile appears more favorable than other popular anesthetic agents. Compared with isoflurane, sevoflurane caused less cytotoxicity and a smaller increase in intracellular calcium, both in vitro9-12 and in infantile mice.13 Compared with propofol, sevoflurane caused less neurotoxicity and no long-term neurocognitive se...
The developing brain begins with an abundance of neurons which must be “physiologically pruned” by programmed cell death or apoptosis.

Early studies in rats have shown with NMDA antagonists that the period of most vulnerability is from birth to day 14 of life, with a peak in sensitivity on day 7.

In rhesus monkeys, with isoflurane, toxicity was most apparent from post conceptual day 122 to postnatal day 5. With ketamine, day 5 was significantly more sensitive than day 30.

In humans, the period of rapid CNS development is from the third trimester and extends through the third year of life. But there is evidence that the 17-20th week PCA, demonstrated the most sensitivity which also correlates to the most vulnerable period for the neurotoxic agent ethanol resulting in fetal alcohol syndrome.
Brain regional vulnerability to anaesthesia-induced neuroapoptosis shifts with age at exposure and extends into adulthood for some regions.

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Abstract
BACKGROUND: General anaesthesia facilitates surgical operations and painful interventions in millions of patients every year. Recent observations of anaesthetic-induced neuronal cell death in newborn animals have raised substantial concerns for young children undergoing anaesthesia. However, it remains unclear why some brain regions are more affected than others, why certain neurones are eliminated while neighbouring cells are seemingly unaffected, and what renders the developing brain exquisitely vulnerable, while the adult brain apparently remains resistant to the phenomenon.

METHODS: Neonatal (P7), juvenile (P21), and young adult mice (P49) were anaesthetized with 1.5% isoflurane. At the conclusion of anaesthesia, activated cleaved caspase 3 (AC3), a marker of apoptotic cell death, was quantified in the neocortex (RSA), caudoputamen (CPu), hippocampal CA1 and dentate gyrus (DG), cerebellum (Cb), and olfactory bulb (GrO) and compared with that found in unanaesthetized littersmates.

RESULTS: After anaesthetic exposure, increased AC3 was detected in neonatal mice in RSA (11-fold, compared with controls), CPu (10-fold), CA1 (three-fold), Cb (four-fold), and GrO (four-fold). Surprisingly, AC3 continued to be elevated in the DG and GrO of juvenile (15- and 12-fold, respectively) and young adult mice (two- and four-fold, respectively).

CONCLUSIONS: The present study confirms the findings of previous studies showing peak vulnerability to anaesthesia-induced neuronal cell death in the newborn forebrain. It also shows sustained susceptibility into adulthood in areas of continued neurogenesis, substantially expanding the previously observed age of vulnerability. The differential windows of vulnerability among brain regions, which closely follow regional peaks in neurogenesis, may explain the heightened vulnerability of the developing brain because of its increased number of immature neurones.
• Clinical Human Data
  
  • Relevant outcome measures

• Confounding variables
  
  • comorbidities

• socioeconomic status

• perioperative physiologic derangements such as fasting, hypothermia, sleep cycles

• hemodynamic instability and the stress response to surgical stimulation
Urologic Study

- 314 children had pediatric urologic procedures between the ages of 0-6 years old
- Parental questionnaires regarding neurobehavioral developmental were sent out, 243 returned
Conclusions

- Children undergoing urologic surgery at age less than 24 months showed more behavioral disturbances than children in whom surgery was performed after age 2

- Post Hoc sample size calculation to reach statistical significance required nearly 6000 patients
Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort

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Background: Anesthetic drugs administered to immature animals may cause neurohistopathologic changes and alterations in behavior. The authors studied association between anesthetic exposure before age 4 yr and the development of reading, written language, and math learning disabilities (LD).

Methods: This was a population-based, retrospective birth cohort study. The educational and medical records of all children born to mothers residing in five townships of Olmsted County, Minnesota, from 1976 to 1982 and who remained in the community at 5 yr of age were reviewed to identify children with LD. Cox proportional hazards regression was used to cal-culate hazard ratios for anesthetic exposure as a predictor of LD, adjusting for gestational age at birth, sex, and birth weight.

Results: Of the 3,357 children in this cohort, 593 received general anesthesia before age 4 yr. Compared with those not receiving anesthesia (n = 4,764), a single exposure to anesthetic-sia (n = 449) was not associated with an increased risk of LD (hazard ratio = 1.0; 95% confidence interval, 0.79–1.27). However, children receiving two anesthetics (n = 104) or three or more anesthetics (n = 44) were at increased risk for LD (hazard ratio = 1.59; 95% confidence interval, 1.06–2.37, and hazard ratio = 2.60; 95% confidence interval, 1.48–4.24, respectively). The risk for LD increased with longer cumulative duration of anesthesia exposure (expressed as a continuous variable) (P = 0.016).

Conclusion: Exposure to anesthesia was a significant risk factor for the later development of LD in children receiving multiple, but not single anesthetics. These data cannot reveal whether anesthesia itself may contribute to LD or whether the need for anesthesia is a marker for other unidentified factors that contribute to LD.

EXPOSURE to alcohol and some anesthetic and sedative drugs cause histopathologic changes in developing brains of animals.1-3 Implicated anesthetics include N-methyl-D-aspartate glutamate receptor antagonists (e.g., ketamine, nitrous oxide) and agents with μ-amino-butyric acid A-mi-metic properties (e.g., pentobarbital, diazepam, isoflurane, halothane, propofol). Some studies suggest that even relatively brief single exposures trigger changes, especially when combinations of agents are used.1-4 In one report, histologic neurodegeneration was associated with a diminished capacity to retain learned behaviors.5 It is not known whether findings in rodent models can be extrapolated to humans, but emerging histologic data in nonhuman pri-mates tend to confirm findings in rodents. These findings have engendered considerable concern among the U.S. Food and Drug Administration and others.6 Except for case series reporting developmental outcomes of critically ill neonates and children undergoing repair of congenital heart disease,7-10 which have multiple limitations, there are no data that can yield insight into whether exposure to anesthesia and surgery during human development causes clinically relevant impairment in neural development.

One challenge to determining whether exposure to anesthesia and surgery in early life impairs neural development is defining relevant outcomes. Learning disabilities (LD) may be an appropriate outcome measure. Children with LD experience problems with one or more of the basic psychological processes involved in understanding or in using spoken or written language, which may manifest itself in an imperfect ability to listen, think, speak, read, write, spell, or perform math-ematical calculations. Because learning disabilities are routinely sought on the basis of standardized individualized testing in educational settings and because of the relatively high incidence rate of LD,11 this outcome is available in large populations and could be assessed.

The purpose of the current study was to determine whether there was an association between exposure to anesthesia and LD in children born between 1976 and 1982.
Mayo Clinic Study - Olmstead County

Initial study:

- compared 593 children with one or more anesthetics before the age of 4 to 4764 children with no exposure

- “…there were significantly more reading, written, language, and math learning disabilities in children who had been exposed to two or more general anesthetics but no increase in disabilities in those exposed to a single anesthetic.”
Mayo Clinic Study - Olmstead County

- Using the same cohort
  - they compared 359 children having an anesthetic before the age of 2 with 5007 non exposed children
  - “…children with two or more exposures were nearly 2 times more likely to be diagnosed with ADHD.”
Mayo Clinic Study - Olmstead County - Limitations

Nearly one-third of the original population migrated away which represents a selection bias because families with ill children having syndromes, chronic diseases and prematurity were more likely to stay within proximity of the Mayo Clinic.

Study adjusted for ASA classes with no change but other confounding factors were not accounted for: maternal and paternal age, level of education and socioeconomic status.

Cohort didn’t account for neonates with 67% of the children exposed were older than one year.
A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children

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635,758 complete New York State Medicaid entries for births between 1999 and 2005
• New York Medicaid Study

• Approximately 9% (60,319) of the children born into New York State Medicaid during this time received a developmental or behavioral diagnosis by the end of 2005, the most common (73.3%) being “developmental delay”
New York Medicaid Study - Initial publication

- Between 1999 and 2005, 383 children prior to age 3 who had undergone hernia repair were compared to a control set of 5050 children adjusting for comorbidities.

- Behavioral outcome was defined as diagnostic codes for I) unspecified delay or behavioral disorder, II) mental retardation, III) autism and IV) language and speech disorder.

- 27.4% carried a diagnosis of a developmental or behavioral disorder compared to the 8% of unexposed children.
New York Medicaid Study between 1999 and 2005 - Second publication:

- 10,450 twin births, 306 had an anesthetic prior to age 3
- 138 discordant twins
- Suggests no causal relationship between anesthesia exposure and brain dysfunction
Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship

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³ Both authors contributed equally to the manuscript

Recent findings of an association between anesthesia administration in the first three years of life and later learning disabilities have created concerns that anesthesia has neurotoxic effects on synaptogenesis, causing later learning problems. An alternative hypothesis is that those children who are likely to undergo surgery early in life have significant medical problems that are associated with a vulnerability to learning disabilities. These two hypotheses were evaluated in a monzygotic concordant-discordant twin design. Data on anesthesia administration and learning abilities and disabilities were available for 1,143 monzygotic twin pairs (56% female) from the Netherlands Twin Registry. Parents of the twins reported on anesthesia use before age 3 and again between ages 3 and 12 years. Near age 12, educational achievement and cognitive problems were assessed with standardized tests and teacher ratings. Results showed that twins who were exposed to anesthesia before age 3 had significantly lower educational achievement scores and significantly more cognitive problems than twins not exposed to anesthesia. However, there was one important exception: the unexposed co-twin from discordant pairs did not differ from their exposed co-twin. Thus, there is no evidence for a causal relationship between anesthesia administration and later learning-related outcomes in this sample. Rather, there is evidence for early anesthesia being a marker of an individual’s vulnerability for later learning problems, regardless of their exposure to anesthesia.

Keywords: anesthesia, learning related problems, MZ discordant design

There has been a persistent concern about the use of anesthesia in young children — specifically those agents that have been shown in histopathological studies to be associated with neurotransptosis and cell death in both in vivo and in vitro studies using laboratory animals (Cattano et al., 2008; Jevtic-Todorovic et al., 2003; Johnson et al., 2008; Olney et al., 2002; Young et al., 2005). Concern about neural development has been raised because many agents used for anesthesia antagonize the N-methyl-d-aspartate glutamate (NMDA) receptor (such as ketamine), stimulate the gamma-aminobutyric acid (GABA) system (such as halothane or the benzodiazepines), or both (such as nitrous oxide) (Mellon et al., 2007). These concerns revolve around the excitotoxic damage that has been demonstrated in relation to the NMDA receptor in prenatal mice and rats (Olney et al., 2002). Demonstration of damage to the regions of the brain important for learning and memory, specifically the hippocampus and dentate gyrus (Ikonomidou et al., 1999), has raised concerns about the effects of NMDA receptor antagonists and GABA agonists on later learning and memory (Jevtic-Todorovic et al., 2003). Some (Levin et al., 1990), but not all (Li et al., 2007), studies have demonstrated that prenatal or early postnatal exposure to anesthesia is associated with later impaired performance on radial arm maze and/or water maze tasks — two tasks known to be associated with hippocampally mediated learning and memory. In non-human primates, there are some data to suggest that similar neurotoxic events can occur with early exposure to these substances (Slikker et al., 2007). There have been referential data that early exposure to anesthesia in humans might have neurotoxic effects. For example, prenatal exposure to cocaine and ethanol, both known to induce apoptotic changes similar to anesthesia (Novikova et al., 2005; Wozniak et al., 2004) may also lead to problems with later learning. Because anesthetic agents work at the level of the synapse, examination has turned to toxic effects of anesthesia exposure during stages of life when synaptogenesis is at its greatest. Earlier case series studies have demonstrated that children who have undergone surgery may be particularly prone to

- Overcomes some of the limitations of prior cohort studies

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Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship

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- Considered twins exposed to anesthetics prior to age 3 and between the ages of 3-12
- Standardized test of “Educational Achievement” at age 12
- 1143 monozygotic twins - 71 discordant twin pairs
Monozygotic twins discordant for anesthetic exposure had equivalent learning-related outcomes.

Interestingly, in male twins, where one had an anesthetic after the age of 3, both siblings had poorer learning-related outcomes than twins never having undergone an anesthetic.
Academic Performance in Adolescence after Inguinal Hernia Repair in Infancy
A Nationwide Cohort Study

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• Danish birth cohort from 1986-1990
• Standardized testing during the 9th grade
• 2,689 exposed compared against 14,575 other children
• After adjustment for confounding variables (birthweight, paternal and maternal age, and education), no statistically significant difference was found.

ABSTRACT

Background: Although animal studies have indicated that general anesthesia 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 subse- quent 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 anal- ysis 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 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 year after adjusting for known confounding fac- tors. However, the higher test score nonattainment rate among the hernia group could suggest that a subgroup of these children are at risk of long-term cognitive impairment after general anesthesia. Further studies are needed.

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.

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**Original Article**

**Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: a nationwide cohort study**

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Keywords
- general anesthesia; neurodevelopment; apoptosis; age; neonates; infants

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**Summary**

**Background:** Immature animals exposed to anesthetics display apoptotic neurodegeneration with subsequent long-term cognitive dysfunctions. Young age at anesthetic exposure is believed to be critical, but human studies are scarce. This study investigated the association between exposure to surgery and anesthesia for pyloric stenosis (PS) before 3 months of age and subsequent educational outcome in adolescence.

**Methods:** This nationwide unselected register-based follow-up study of the Danish birth cohorts 1986–1990 compared the educational outcome of all children having undergone surgery for PS before 3 months of age with a randomly selected, age-matched 5% sample of the same cohort. Primary analysis compared the average test scores at ninth grade adjusting for gender, birth weight, and parental age and education. Secondary analysis compared the proportions not attaining the test scores between the two groups.

**Results:** The exposure group comprised 779 and the control group consisted of 14,665 individuals. Although the exposure group performed lower than the control group (average score 0.17 lower, 95% CI: 0.08–0.25), after adjusting for known confounders, no statistically significant difference (—0.04, 95% CI: —0.09 to 0.08) between the 2 groups could be demonstrated. However, we found an odds ratio (OR) for test score nonattainment-associated PS repair of 1.37 (95% CI: 1.11–1.68).

**Conclusion:** Children operated for PS before 3 months of age have educational performance tests similar to the background population at age 15–16 years after adjusting for known confounders. The higher nonattainment rate could suggest that a subgroup of PS children is developmentally disadvantaged.

**Introduction**

There is a strong and accumulating evidence that exposures to virtually all general anesthetics early in life causes increased neuroapoptosis with later deficits in learning ability in laboratory animals, including nonhuman primates (1–4). The detrimental effect appears to be strongly age dependent, in that the neurotoxic impairment is most severe if the exposure occurs at the time of peak synaptogenesis (4). How these findings translate into a human context remains unknown, but it is generally assumed that this correlates with neonates, infants, children with an anesthetic prior to 3 months of age also compared to 14,665 other children.

- **Danish birth cohort from 1986-1990**
- **Standardized testing during the 9th grade**
- **779 children with an anesthetic prior to 3 months of age also compared to 14,665 other children**
- **After adjustment for confounding variables (birthweight, paternal and maternal age and education), no statistically significant difference was found.**
Regarding both Danish Cohort studies

All of the above mentioned confounders more strongly affected academic achievement than surgery and anesthesia
Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia

WHAT’S KNOWN ON THIS SUBJECT: Immature animals exposed to anesthetics display apoptotic neurodegeneration and long-term cognitive deficiencies. In children, studies of cognitive deficits associated with anesthesia exposure have yielded mixed results. No studies to date have used directly administered neuropsychological assessments as outcome measures.

WHAT THIS STUDY ADDS: This study examines the association between exposure to anesthesia in children under age 3 and deficits at age 10 by using a battery of directly administered neuropsychological assessments, with deficits found in language and abstract reasoning associated with exposure.

abstract

BACKGROUND: Over the past decade, the safety of anesthetic agents in children has been questioned after the discovery that immature animals exposed to anesthesia display apoptotic neurodegeneration and long-term cognitive deficiencies. We examined the association between exposure to anesthesia in children under age 3 and outcomes in language, cognitive function, motor skills, and behavior at age 10.

METHODS: We performed an analysis of the Western Australian Pregnancy Cohort (Raine) Study, which includes 2868 children born from 1989 to 1992. Of 2608 children assessed, 321 were exposed to anesthesia before age 3, and 2287 were unexposed.

RESULTS: On average, exposed children had lower scores than their unexposed peers in receptive and expressive language (Clinical Evaluation of Language Fundamentals: Receptive [CELF-R] and Expressive [CELF-E]) and cognition (Colored Progressive Matrices [CPM]). After adjustment for demographic characteristics, exposure to anesthesia was associated with increased risk of disability in language (CELF-R: adjusted risk ratio [aRR], 1.87; 95% confidence interval [CI], 1.20–2.93; CELF-E: aRR, 1.72; 95% CI, 1.12–2.64), and cognition (CPM: aRR, 1.69; 95% CI, 1.13–2.53). An increased aRR for disability in language and cognition persisted even with a single exposure to anesthesia (CELF-R aRR, 2.41; 95% CI, 1.40–4.17, and CPM aRR, 1.73; 95% CI, 1.04–2.90).

CONCLUSIONS: Our results indicate that the association between anesthesia and neuropsychological outcome may be confined to specific domains. Children in our cohort exposed to anesthesia before age 3 had a higher relative risk of language and abstract reasoning deficits at age 10 than unexposed children. Pediatrics 2012;130:e476–e485

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KEY WORDS
anesthesiology, neurodevelopmental, cognitive function, neurotoxicity, language development

ABBREVIATIONS
aRR—adjusted risk ratio
CBCL—Child Behavior Checklist
CELF—Clinical Evaluation of Language Fundamentals
CELF-R—Clinical Evaluation of Language Fundamentals Receptive language score
CELF-E—Clinical Evaluation of Language Fundamentals Expressive language score
CELF-T—Clinical Evaluation of Language Fundamentals Total language score
CI—confidence interval
CPM—Raven’s Colored Progressive Matrices MAND—McGraw Assessment of Neuromuscular Development PPVT—Peabody Picture Vocabulary Test SDMT—Symbol Digit Modalities Test

Dr S Ing, DiMaggio, Whitehouse, Hegarty, von Ungern-Sternberg, Davidson, Wood, Li, and Sun conceived and designed the study; Drs Whitehouse, Hegarty, von Ungern-Sternberg, and Davidson analyzed the data; Drs Ing, DiMaggio, Whitehouse, Hegarty, von Ungern-Sternberg, Davidson, Wood, Li, and Sun interpreted the data; Dr Ing wrote the article, which was critically reviewed by Drs Ing, DiMaggio, Whitehouse, Hegarty, von Ungern-Sternberg, Davidson, Wood, Li, and Sun; Dr Ing and Ms Brady performed the statistical programming; and all authors reviewed and approved the final report.
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CI—confidence interval
CPM—Raven's Colored Progressive Matrices
MAND—McCaron Assessment of Neuromuscular Development
PPVT—Peabody Picture Vocabulary Test
SDMT—Symbol Digit Modalit Test

Dr Ing, DiMaggio, Whitehouse, Hegarty, von Ungern-Sternberg, Davidson, Wood, Li, and Sun conceived and designed the study; Drs Whitehouse, Hegarty, von Ungern-Sternberg, and Davidson reviewed and interpreted the data; Dr Ing wrote the article, which was critically reviewed by Drs Ing, DiMaggio, Whitehouse, Hegarty, von Ungern-Sternberg, Davidson, Wood, Li, and Sun; Dr Ing and Ms Brady performed the statistical programming; and all authors reviewed and approved the final report.

• Noted statistical significance in learning disabilities compared to non exposed children

• Did not account for significant co-morbidities
Behavior and Development in Children and Age at the Time of First Anesthetic Exposure

Cor J. Kalkman, M.D., Ph.D.,* Linda Paelinck, M.Sc.,† Karel G. Moons, Ph.D.,* Morina Veenhuizen, Marcel Bruns, R.N.,§ Gerben Strijers, Ph.D.,∥ Tom P. de Jong, M.D., Ph.D.‡

Early Childhood Exposure to Anesthesia and Risk of Developmental and Behavioral Disorders in a Sibling Birth Cohort

Charles DiMaggio, PhD,
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Academic Performance in Adolescence after Inguinal Hernia Repair in Infancy

A Nationwide Cohort Study

Tom G. Hansen, M.D., Ph.D.,* Jacob Dorchio A. Pedersen, M.Sc.,† Jeffrey Kaare Christensen, M.D., Ph.D., D.M.

Education outcome in adolescence following pyloric stenosis repair before 3 months of age: a nationwide cohort study

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• Ongoing prospective studies:

  • Pediatric Anesthesia and Neuro-Development Assessment Study

    • 500 ASA 1 and 2 children for inguinal hernia repair before the age of 3

    • extensive neuro developmental testing between the ages of 8 and 15

  • GAS study

    • Multi-center, randomized controlled children undergoing inguinal hernia repair prior to the age of 60 weeks post-conceptual age randomized to either general or regional anesthesia

    • Enrollment completed, follow-up time is 5 years with final analysis available in 2017
San Francisco – November 10, 2015 – SmartTots today released a supplement to their recently updated Consensus Statement. Immediately following the announcement of the secondary outcomes from the clinical trial, General Anesthesia Compared to Spinal Anesthesia (the GAS Study), SmartTots convened more than 30 experts in anesthesia, pediatric medicine and neuroscience to discuss the trial’s early findings and consider their significance. The Consensus Statement Supplement was developed as a result of this meeting.

The GAS Study is the first prospective clinical trial to explore the effects of anesthetics on the developing brain in humans. The secondary outcome data, based on 532 subjects, indicated that children who had undergone either general anesthesia or regional anesthesia in a surgical procedure lasting less than 1 hour showed no difference in cognitive development at the 2-year timepoint.

While acknowledging the importance of the research, SmartTots is emphasizing that these findings represent secondary outcomes. The primary outcome of the GAS Study will be performance on a test of cognition at age 5, and may be able to detect changes not present at age 2.

While the results are welcome and encouraging, important questions still remain. It is too soon to say with certainty that a single short duration of exposure is safe. SmartTots continues to work with investigators to design and promote additional research. In the meantime, SmartTots does not recommend putting off needed surgery or procedures requiring anesthetics or sedatives – or conducting needed treatments without pain medication. SmartTots urges health care providers and parents to discuss the risks, benefits and timing of any treatment, and advises weighing the benefits of any elective procedure against potential risks from anesthesia and sedation.
Consensus Statement on the Use of Anesthetic and Sedative Drugs in Infants and Toddlers

October 2015

Each year, millions of infants and toddlers require anesthesia and/or sedation for surgery, procedures, and tests. Concern has been raised about the safety of the medicines used for anesthesia and sedation in young children. This concern is based on research in animals demonstrating long-term, possibly permanent, injury to the developing brain caused by exposure to these medicines. This injury results in abnormalities in behavior, learning, and memory in animals. The effect of exposure to anesthetic drugs in young children is unknown; however, some but not all studies have suggested that problems similar to those seen in animals could also occur in infants and toddlers. It is important to recognize that the studies in children suggest that similar deficits may occur. These studies in children have limitations that prevent experts from understanding whether the harmful effects were due to the anesthetic drugs or to other factors such as the surgery or related illness. Better research is required to understand whether children are harmed and if so, what alternative medicines might be used to minimize risk from anesthesia.

Because there is not enough information about the effects of anesthetic drugs on the brains of young children, it is not yet possible to know whether use of these medicines poses a risk, and if so, whether the risk is large enough to outweigh the benefit of the planned surgery, procedure, or test. Until further research clarifies the importance of these findings we recommend:

For healthcare providers

Answers to questions from parents and caregivers related to these risks should highlight the differences between research findings in animals and children and the uncertainty of any effect in children. It may also be emphasized that because most anesthetic drugs have been shown to cause injury in animal experiments, no specific medications or technique can be chosen that are safer than any other. Clearly, anesthetic drugs are a necessary part of the care of children needing any surgery, procedure, or test that cannot be delayed. Decisions regarding the timing of a procedure requiring anesthesia should be discussed with all members of the care team as well as the family or caregiver before proceeding. The benefits of an elective procedure should always be weighed against all of the risks associated with anesthesia and surgery.

For parents and caregivers

Discuss the timing of planned procedures with your child’s primary care physician, surgeon/proceduralist and anesthesiologist. Concerns regarding the unknown risk of anesthetic exposure to your child’s brain development must be weighed against the potential harm associated with cancelling or delaying a needed procedure. Each child’s care must be evaluated individually based on age, type and urgency of the procedure and other health factors. Your child’s doctors are best able to provide this advice. If you desire additional information and updates on current research, please go to smarttots.org.