Does general anesthesia affect neurodevelopment in infants and children?

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ABSTRACT

General anesthesia has been unequivocally linked to abnormal development of the central nervous system, leading to neurocognitive impairments in laboratory models. In vitro and in vivo studies have consistently shown that exposure to GABA agonists (e.g., volatile anesthetics, midazolam, and propofol) or NMDA antagonists (e.g., ketamine, isoflurane, and nitrous oxide) produces dose dependent and developmental age dependent effects on various neuronal transmission systems. Exposure to these drugs increases neuronal cell death in juvenile animals including rats, mice, and non-human primates. The possibility of anesthetic induced neurotoxicity occurring in children has led to concerns about the safety of pediatric anesthesia. A spectrum of behavioral changes has been documented after general anesthetic exposure in young children, including emergence delirium, which may be evidence of toxicity. Most clinical studies are retrospective; specifics about medications or monitoring are unavailable and many of the outcomes may not be sensitive to detect small neurocognitive deficits. Some of these retrospective studies have shown an association between anesthesia exposure at a young age and neurocognitive deficits, but others have not. Practitioners and families should be reassured that although general anesthetics have the potential to induce neurotoxicity, very little clinical evidence exists to support this.

Introduction

General anesthesia has been unequivocally linked to abnormal development of the central nervous system, leading to neurobehavorial impairments in laboratory models.1 2 The possibility of anesthetic induced neurotoxicity occurring in children has led to concerns about the safety of pediatric anesthesia. General anesthetics administered to induce altered states of consciousness meet the definition of neurotoxins. The US National Center for Toxicologic Research, a division of the Food and Drug Administration (FDA), defines neurotoxicity as any adverse effect on the structure or function of the central and/or peripheral nervous system by a biologic, chemical, or physical agent that causes any alteration from baseline that diminishes the ability of an organism to survive, reproduce, or adapt to its environment.3 Furthermore, the neurotoxic effects may be caused by direct or indirect actions on the nervous system, and may be reversible or permanent. General anesthesia is usually considered a reversible medically induced coma, but it is possible that there may be subtle irreversible effects.

This review examines the evidence for the neurocognitive and functional effects of commonly used anesthetics in laboratory models and evaluates its relevance to clinical care in pediatric patients. The target audience for this review includes surgeons, pediatricians, and other healthcare providers involved in the care of young children. We present a brief overview of the animal data that has shown anesthetic induced neurotoxicity, and the clinical data that are equivocal in demonstrating anesthetic induced neurotoxicity. We also present the spectrum of behavioral changes in young children documented after their exposure to general anesthetic, including emergence delirium, which may be evidence of toxicity. In addition, we aim to reassure practitioners that although general anesthetics have the potential to induce neurotoxicity, there is little evidence of long term anesthetic neurotoxicity in children.

Sources and selection criteria

We performed a PubMed search from January 1946 through June 2019 to identify English language articles published in peer reviewed journals by using the following search terms: “anesthetic”, “neurotoxicity”, “anesthetic neuroapoptosis”, “infants, children, anesthesia”, “sevoflurane”, “isoflurane”, “ketamine”, “dexamethasone”, “postoperative delirium”, “postoperative agitation”, “delirium, anesthetic recovery”, “cholinergic agents”, “neurodevelopment,
academic achievement, cognitive development", “surgery, infants, prenatal.” We also identified references from relevant review articles, as well as from the similar items section of PubMed. We primarily reviewed articles that focused on humans, since a recent systemic review of the laboratory data comprehensively detailed the relevant reports and we elected not to duplicate this exercise. For clinical reports, we prioritized randomized prospective trials but also included retrospective cohort and database studies. We prioritized large cohort studies over small, and have presented the results by time of exposure. We excluded articles published in non-peer reviewed journals or those not available in PubMed. We also included consensus statements, guidelines, and systematic reviews published in the past 10 years. Only public statements from the FDA and consensus panels from the European Society of Pediatric Anesthesia were cited in this review.

Pre-clinical studies
Characterization
The immature brain undergoes some baseline neurodegeneration by apoptotic processes as part of normal development. The sentinel report of accelerated neurodegeneration in rat pups exposed to N-methyl-D-aspartate (NMDA) antagonists generated ongoing investigations on anesthetic induced developmental neurotoxicity. Subsequent in vitro and in vivo studies have consistently shown that exposure to GABA agonists (eg, volatile anesthetics, midazolam, and propofol) or NMDA antagonists (eg, ketamine, isoflurane, and nitrous oxide) produces dose dependent and developmental age dependent effects on various neuronal transmission systems and increases neuronal cell death. Perinatal exposure to anesthetic and sedative drugs leads to abnormal neuroapoptosis and stunted dendritic growth. While administration of anesthetics to juvenile rats leads to enhanced dendritic formation and synaptic density, the clinical significance for this finding is unknown. Similar aberrant dendritic morphology has been observed in psychiatric and neurological disorders. Dexmedetomidine has been shown to mitigate the neuroapoptotic effect of isoflurane in some models. However, subsequent investigations utilizing higher dosing schedules did not consistently show a neuroprotective effect.

Neurodevelopmental impairments in learning, memory, attention, emotional behavior, psychomotor speed, concept formation, motivation, emotional behaviors, and motor function, have been demonstrated in several experimental models in neonatal rats, mice, guinea pigs, and rhesus monkeys. Non-human primates exposed to anesthetics during infancy exhibit abnormalities in emotional reactivity such as increased anxiety at being exposed to strangers.

Emerging animal data show that repeated exposure to general anesthesia during infancy can initially appear to not affect development, but later testing reveals deficits. Rhesus monkeys exposed repeatedly to sevoflurane during early infancy develop visual memory deficits that only emerge after the first year of life.

Mechanisms
General anesthesia removes sensory input and suppresses normal neural traffic, which in turn diminishes the trophic support required for neurogenesis and context dependent modulation of neuroplasticity. However, several lines of investigation have also implicated neuronal cell death mechanisms such as excitotoxicity, mitochondrial dysfunction, aberrant cell cycle re-entry, trophic factor dysregulation, and disruption of cytoskeletal assembly. GABA acts as an inhibitory agent in the mature brain, but many preclinical studies have found it to be an excitatory agent during early stages of brain development. The immature NA/K/2Cl transporter protein NKCC1 produces a chloride influx leading to neuron depolarization. As a consequence, GABA remains excitatory until the mature chloride transporter KCC2 is expressed, which actively transports chloride out of the neuronal cell. This switch begins at around 15 weeks after birth in term human infants, but is not complete until about 1 year of age. Sevoflurane has produced seizures and apoptotic neuronal cell death in a neonatal rodent model. Blockade of the NKCC1 channel by bumetanide mitigates this excitotoxic response. Several non-specific drugs that have neuroprotective properties (lithium, melatonin, estrogen, erythropoietin, estradiol, and dexmedetomidine) have been shown to alleviate anesthetic induced developmental neurotoxicity in non-human animals. Furthermore, an enhanced and stimulating environment mitigates neurobehavioral deficits after neonatal exposure to sevoflurane.

Finally, anesthetics alter epigenetic modulation of transcription, which clearly demonstrates a global effect on neurodevelopment and synaptogenesis. Neonatal male rats born to mothers who were exposed to sevoflurane before pregnancy have reduced expression of the KCC2 gene. This gene has been implicated in the development of autism spectrum disorders in humans.

Translation of pre-clinical studies into a clinical context
A meta-analysis of more than 400 preclinical reports showed no clear threshold of exposure duration below which no structural injury or subsequent cognitive abnormalities occurred, or a specific age of vulnerability. However, most preclinical studies demonstrate anesthetic induced neurotoxicity only after four hours or more of general anesthesia, which suggests that most children are not at risk, since anesthetics during childhood are typically shorter in duration.
have a much longer duration than in animals such as rats whose lifespan is only two years. Although the first 24 months are considered critical for visual development in humans, treatment for amblyopia has been successful in some children even after the age of 8, demonstrating the potential for plasticity of the human brain throughout the lifespan. Preclinical studies in very young animals have shown diffuse injury and functional deficits in learning and memory, which may mean that humans would expect to exhibit lower intelligence quotients, behavioral problems, impaired cognitive function, and ultimately impaired executive function.

Thirdly, it is unknown whether certain subpopulations of animals are more susceptible to anesthetic induced neurotoxicity. Human subpopulations appear to be differentially affected by anesthetic exposures as they age, therefore it is important to determine whether children exhibit similar differentiations. For example, older patients who experience challenges in daily living have a higher rate of postoperative neurocognitive dysfunction and postoperative delirium compared with able older patients. Clinical studies

Several perioperative factors other than anesthetic exposure may alter postoperative cognition and behavior. Inflammatory responses to surgery can induce neurocognitive dysfunction in adults even when only local anesthesia is used. The stress of hospitalization, especially intensive care, can induce similar neurocognitive dysfunction in adults. These factors have not been studied in children. Many congenital anomalies in children involve multi-organ systems including the brain, possibly putting these infants at higher risk during general anesthesia. Infants born with major cardiac defects, even when born at term, have a developmentally immature brain because of anatomic alterations in fetal cerebral blood flow, which raises the risk of white matter injury during general anesthesia.

Immediate postoperative neurocognitive changes: emergence delirium

Emergence delirium occurs typically in the post-anesthesia care unit, and usually lasts 10–30 minutes in young children. Emergence delirium has been described as a dissociated mental state in which the child is inconsolable, irritable, uncooperative, and may be thrashing, crying, moaning, or incoherent. It occurs in 5% to 10% of adult patients, but is found in up to 80% of some pediatric patient populations. The incidence of emergence delirium after halothane, isoflurane, sevoflurane, and desflurane ranges from 2% to 55%. It is more common in children under 5 or in adults over 65. The causes of emergence delirium are probably multifactorial. Proton magnetic resonance spectroscopy, which measures brain metabolism, has shown that general anesthesia with sevoflurane increases neuronal activity and increases emergence delirium in children. Electroencephalogram (EEG) evidence for a cohort of children undergoing sevoflurane anesthesia showed that the children with emergence delirium had a prolonged state with low voltage, fast frequency activity at emergence, which later converted to normal sleep-like EEG patterns.

In young children, the most predictable factor for emergence delirium is the type of general anesthetic used. Most anesthetic drugs have been implicated, including volatile anesthetics, benzodiazepines, ketamine, barbiturates, and propofol, as well as atropine, scopolamine, and droperidol. The two anesthetics most commonly associated with emergence delirium are sevoflurane and desflurane. One suggested explanation for this is the rapid emergence from these agents; however, the incidence of emergence delirium after propofol anesthetics, which have equally rapid emergence, is much less. Postoperative pain has also been implicated as a risk factor for emergence delirium.

Emerging treatments for emergence delirium

Intraoperative treatment with analgesics has been shown to reduce the incidence of emergence delirium in young children, leading to the hypothesis that inadequately treated pain may be a causative factor. Studies have shown that intranasal fentanyl administered intraoperatively decreases the incidence of emergence delirium after myringotomy surgeries in young children. Emergence delirium is commonly seen in young children with known effective regional anesthesia blockade (epidural and caudal) suggesting that the effect of the analgesics in some cases may be to delay emergence rather than alleviate pain. A small randomized trial found that an infusion of dexmedetomidine (0.2 µg/kg/min) compared with placebo significantly decreased the incidence of emergence delirium in children aged 1-10 who had received a sevoflurane based anesthetic (26% in the dexmedetomidine group vs 60.8% in the control group, P = 0.036). Altering the anesthetic technique from a primarily volatile anesthetic to total intravenous anesthesia with propofol has been shown to decrease the incidence of emergence delirium in children, and thus should be considered especially in patients who have already experienced emergence delirium after a previous general anesthetic.

For most children, treatment for emergence delirium is unnecessary other than support and prevention from harm. Any child with postoperative agitation should be monitored to determine whether they have emergence delirium or another potentially harmful cause of agitation, such as hypoxia, hypotension, hypercarbia, or hypoglycemia. Other common causes of agitation in the post-anesthesia care unit include inadequately treated pain and anxiety over parental separation, which are usually easily remediated.
Long term effects in childhood of general anesthetic exposure

Many clinical studies have been made of the long term effects of anesthesia, but most are retrospective in nature and in many, the data originally collected were for a different scientific inquiry. Often, specifics about the anesthetics such as medications or monitoring used are unavailable for study and many of the outcome measures are not sensitive enough to detect small differences. Furthermore, children may not exhibit deficits until later in their development. In addition, the category of patient and/or procedure being studied matters. For example, children undergoing cleft lip and palate procedures are at risk for hearing difficulties, and children undergoing ophthalmologic procedures are at risk for poor vision, which may negatively affect their development.

Outcome measures for assessing development

Outcome measures for clinical studies in children exposed to general anesthesia can be broadly divided into three types. Some studies have reported academic performance or school readiness tests; others have reported the incidence of medical or educational interventions for neurodevelopmental or behavioral issues. Some studies have reported the results of individual validated neuropsychologic testing.

A broad based academic performance test might include national educational achievement scores such as the IOWA Assessments, whose primary goal is to learn about the skills of individual students to aid in curriculum planning. School readiness tests include the Early Development Instrument, a validated, population based measure of early child development, which every child in Canada takes before entering kindergarten.

Medical or educational determination of neurodevelopmental or behavioral problems can be measured by medical diagnoses and billing codes or by reported school referrals for learning disabilities.

The most commonly used neuropsychologic tool to assess the development of infants and toddlers is the Bayley Scales of Infant and Toddler Development which is used in children of 1-42 months. This test has been found to be sensitive to adverse neurodevelopmental effects of a variety of risk factors and exposures.58-60 In older children the Wechsler Preschool and Primary Scale of Intelligence, which is designed for children aged 2 years and 6 months to 7 years and 7 months, provides a composite score of intelligence as well as subscores in verbal and performance cognition.

We have chosen to present these studies by age of anesthetic exposure and, where possible, to group studies by authors and by age at outcome measure. Cohort studies are presented by year of cohort birth. Only one randomized controlled trial was included, and was designed to study anesthetic induced neurotoxicity in infants less than 6 months of age.

Exposure at ≤6 months

Very premature infants undergoing laparotomy for necrotizing enterocolitis or patent ductus arteriosus repair have poorer neurocognitive outcomes compared with those that are medically managed.61 62 In infants surgically treated for tracheoesophageal fistula repair or congenital diaphragmatic hernia repair, up to 50% will require early intervention services.63 64 A meta-analysis of 511 non-syndromic neonates (13 studies) born with non-cardiac congenital abnormalities treated surgically found that 23% (range 3.56%) of patients had a delay in cognitive development as measured by the Bayley Scales of Infant development at age 12 or 24 months, and 25% (range 0.77%) had a delay in their motor development.35

Infants undergoing cardiac surgery are at high risk for later neurocognitive delays. A retrospective cohort study of 59 infants found an association between volatile anesthetic exposure during neonatal cardiac surgery (coefficient −1.26, 95% confidence interval −2.37 to −0.14) but another cohort study of 95 infants undergoing cardiac surgery found no evidence of an association between the cumulative exposure to sedatives/general anesthesia and adverse neurodevelopment.65 66

A Danish cohort study comparing 779 infants <3 months exposed to general anesthesia for pyloric stenosis repair with a randomly selected age matched control consisting of 5% of the total cohort (14,665 individuals) found no statistically significant difference (−0.04, 95% confidence interval −0.09 to 0.08) between the two groups on educational performance testing at age 15-16 years, after adjusting for known confounders.67

The GAS Trial is a randomized controlled trial comparing the neurocognitive outcomes of 722 infants <60 weeks postmenstrual age exposed to either general sevoflurane anesthesia or awake spinal or epidural anesthesia for inguinal hernia repair. It found no statistically significant difference (0.169, 95% confidence interval −2.30 to 2.64) in the Bayley 3 cognitive scores done at age 2.68 There were also no statistically significant differences in the other domains, language, motor, social, emotional, and adaptive behavior. The primary outcome results (full scale IQ done at age 5) confirmed there were no statistically significant differences (0.23, 95% confidence interval −2.59 to 3.06) on the full scale intelligence quotient on the Wechsler Preschool and Primary Scale of Intelligence.69 The average duration of the surgery and anesthesia in this study was less than one hour.70

Exposure <1 year

In Iowa, school achievement scores for 287 children who had inguinal herniorrhaphy with or without orchidopexy, pyloromyotomy, or circumcision at <1 year were compared with norms for age.71 In this retrospective cohort study, the mean composite score was 43+/−22.4, which was statistically significantly lower than the expected normative
value of 50, and 12% of children had scores below the 5th percentile. However, in a subset analysis of children in this cohort who had no central nervous system abnormalities or other risk factors for poor neurocognitive development, the mean score was 47.6+/−23.4, which was not statistically significantly different from the expected population mean, but the proportion of scorers below the 5th percentile was 14%. 

A retrospective study from Vermont examined a similar patient population (265 infants with the same procedures) and found no relation between duration of exposure to spinal anesthesia on mathematics and reading standardized testing (n=246; r=−0.04 mathematics; P=0.57 n=257; r=−0.02; P=0.73 reading) suggesting that spinal anesthesia does not affect neurocognitive development.

In Singapore, a retrospective cohort study comparing 100 children <1 year who were exposed as infants to general anesthesia for minor surgery with an aged matched control group of 106 children found the odds of a diagnosis of learning disability by age 12 were 4.5 (95% confidence interval 1.44 to 14.1) times greater in the exposed group than in controls. However, the study found no clinically relevant difference in Singapore standardized Primary School Leaving Examination scores.

A retrospective Danish cohort study examining 2689 infants <1 year who were exposed to general anesthesia for inguinal herniorrhaphy found no difference after adjusting for known confounders (−0.04, confidence interval −0.09 to 0.01) in exposed and control children in their academic performance at their Danish achievement testing done in the 9th grade (age 15-16 years).

**Exposure ≤2 years**

A retrospective propensity matched cohort study in which 350 exposed children were matched with 700 children from a cohort of 5357 children born between 1976 and 1982 in Minnesota examined the risk factors for attention deficit/hyperactivity disorder (ADHD). After adjusting for gestational age, sex, birth weight, and comorbid health conditions, exposure to multiple but not to single general anesthetics increased the risk (hazard ratio 2.12, 95% confidence interval 1.26 to 3.54) of learning disability and lower achievement scores, but not the likelihood of referral for an individual education plan.

Another retrospective Danish cohort study of children born between 1986 and 1990 compared 558 children with a 5% sample of the total cohort of 14677 children and examined the role of timing of anesthetic exposure on young children treated for cleft lips, cleft palates, and both cleft lips and palates. The study found that the oral cleft type was associated with poorer academic performance rather than number and timing of anesthesia and operations. Interestingly, children born with cleft lip and cleft palate whose median age at exposure was 2.8 months were not statistically significantly different on school achievement scores, but children who were treated for isolated cleft palate at a median age of 22 months had lower achievement scores (mean difference −0.20, 95% confidence interval −0.38 to −0.03) compared with controls.

**Exposure >2 years**

A monozygotic concordant-discordant twin design study attempted to control for confounding by prior pathology, socioeconomic factors, and the effects of surgery in 1143 monozygotic twin pairs. This study found that male twins in which one or more infants of the twin pairs were exposed before the age of 3 had lower educational achievement scores (mean difference −2.27, p =0.04) than discordant unexposed twin pairs. However, no differences were observed between discordant twin pairs, suggesting that there was no causal relation between anesthesia exposure and later learning difficulties.

Several retrospective cohort studies have utilized the prospective Western Australian Pregnancy (Raine) cohort of children, which originally was created to examine the possible neurocognitive effects of prenatal ultrasonography. This cohort includes 2868 children born between 1989 and 1992, of whom 321 were exposed to general anesthesia before the age of 3. Neurocognitive assessments at age 10 found that exposure to anesthesia was associated with increased risk of disability in language (receptive language: adjusted risk ratio, 1.87; 95% confidence interval 1.20 to 2.93, expressive language: adjusted risk ratio 1.72; 95% confidence interval, 1.12 to 2.64), and cognition (cognition: adjusted risk ratio 1.69; 95% confidence interval 1.13 to 2.53). Subgroup analysis of 781 children found that exposed children had a higher rate of abnormal neuropsychologic testing and clinical disorders diagnoses but no differences (adjusted risk ratio 1.27; 95% confidence interval 0.93 to 1.73) in academic achievement. Using the Raine cohort, the study explored the relation between duration of volatile anesthetic exposure and neurodevelopment. It was found that children having procedures that lasted longer than 35 minutes had more language difficulties compared with those having shorter procedures, or with unexposed children.

Several studies identified behavioral and developmental disorders as coded in medical bills as outcome measures. A retrospective analysis of 383 children who underwent inguinal hernia repair in the first three years of life was compared with a sample of 5050 children frequency matched on age from a database of 93317 children. After controlling for age, gender, and complicating birth related conditions, the exposed children were more than twice (adjusted hazard ratio 2.3, 95% confidence interval 1.3 to 4.1) as likely to be diagnosed with a behavioral or developmental disorder as the comparison group. From this same sample, a retrospective cohort of 10450 siblings born between 1999 and 2005 was constructed. The exposed group was 304 children who underwent general anesthesia before the age of 3 who were compared with 10146
unexposed children. Hazard ratios for a behavioral or developmental issue after adjustment for gender and history of birth related medical conditions was 1.6 overall (95% confidence interval 1.4 to 1.8) with increasing risk for two or more operations. However, within a subgroup of 138 matched sibling pairs, the relative risk was 0.9 (95% confidence interval 0.6 to 1.4), perhaps indicating the importance of family environment.

A retrospective study of a matched cohort from the National Health Insurance Research Database of Taiwan examined the risk of attention deficit/ hyperactivity disorder development in 16,465 children born between 2001 and 2005, of whom 3,293 were exposed to general anesthesia before the age of 3. This study found no increased adjusted hazard ratio (1.06, 95% confidence interval 0.86 to 1.31) of developing ADHD in children who had single or multiple anesthetic exposures.  

The PANDA study reported on the association between a single general anesthetic exposure before the age of 36 months and neurocognitive outcomes by psychometric testing in later childhood. This ambidirectional study developed a sibling matched cohort of 105 sibling pairs in whom one of the siblings had been exposed to general anesthesia for inguinal hernia repair before the age of 3. The median time of the procedure was 80 minutes and the exposed siblings were disproportionately male (90% v unexposed 56%). There were no differences in mean IQ (full scale IQ= −0.2, 95% confidence interval −2.6 to 2.9); performance IQ (performance IQ= 0.5, 95% confidence interval −2.7 to 3.7); and verbal IQ (verbal IQ= −0.5, 95% confidence interval −3.2 to 2.2).  

The Mayo Anesthesia Safety in Kids (MASK) study, which evaluated a cohort of 997 children who were exposed to general anesthesia before the age of 3, showed negligible deficits in singly exposed patients. However, children who had multiple exposures to anesthesia and surgery had impairments in processing speed and fine motor abilities, but not statistically significant reductions in their IQ (multiple exposed IQ: 1.3 points, 95% confidence interval −3.8 to 1.2) and (single exposed IQ: 0.5 points, 95% confidence interval −2.8 to 1.9) as the primary outcome measure compared with propensity matched controls. However, a secondary analysis of a subset of multiply exposed patients revealed a pattern of deficits in several neuropsychological tests. Analysis was done by cluster, with the odds of multiply exposed children belonging to the lowest performance cluster being 2.83 (95% confidence interval 1.49 to 5.35) compared with belonging to middle cluster. The operant test battery (a task based assessment that has high correlation with color and position discrimination accuracy and IQ scores in children) has demonstrated deficits in non-human primates exposed to ketamine. The operant test battery was applied to the patient cohorts in the MASK study and did not detect a difference between the control and exposed groups using a similar cluster analysis based on test performance.

**Exposure 4 years**

In the original cohort of 5,357 children from the Mayo Clinic in Minnesota born between 1976 and 1982, 593 had been exposed to general anesthesia before the age of 4. A single exposure to general anesthesia was associated with no increased risk of cumulative learning disabilities, but children exposed to two or more (n=144) had almost double the risk (hazard ratio of 2 exposures:1.59; 95% confidence interval 1.06 to 2.37, and hazard ratio of 3 or more exposures:2.60; 95% confidence interval 1.60 to 4.24) of unexposed children. The risk of learning disabilities also increased with longer cumulative duration of anesthesia exposure. A criticism of this study was that this cohort of children had anesthesia before pulse oximetry was adopted and before sevoflurane was used.

A follow-up report involved a propensity matched study of 1,057 children born between 1996 and 2000 and aged less than 3 when they were exposed to general anesthesia. It found that they had roughly double the risk of learning difficulties with more than one exposure (hazard ratio: 2.17, 95% confidence interval 1.32 to 3.59).

Two large epidemiologic studies from Canada used the Early Development Instrument (EDI), a 104 component questionnaire encompassing five developmental domains, which is completed in kindergarten to determine school readiness as an outcome measure. In Manitoba, 18,056 children were studied, of whom 3,850 had been exposed to a single general anesthetic and 620 had been exposed to two or more general anesthetics. The authors examined exposures before the age of 2 and from ages 2-4. They found no association using mixed regression modeling between single or multiple general anesthetic exposures and deficits, but found a modest increase in risk for single exposures in children aged 2 to 4, most notably in the domains of communications/general knowledge and language/cognition. A similar study was done examining the children of Ontario and using the EDI as an outcome measure. In this cohort, the primary outcome of interest was any domain of the EDI in the lowest 10th percentile for the population. Subgroup analyses were performed based on the age of first surgery (less than 2 years or from 2-4 years). The Ontario cohort was large, with 18,857 children of whom 28,366 underwent general anesthesia before completion of the EDI.

An early developmental vulnerability was detected in the exposed group, but the effect was modest, with an adjusted odds ratio of 1.05 (95% confidence interval, 1.01 to 1.08). Subgroup analysis found no increase in vulnerability in children under 2 at the time of first exposure, and no increase in odds of early developmental vulnerability with frequency of exposure.
A large Swedish study examined the association of anesthesia and surgery before age 4 and long term academic and cognitive performance, by indexing school grades at age 16 and using IQ test scores at age 18 at military conscription. The cohort of 2,174,073 children were born between 1973 and 1993. Of this cohort, 33,514 children had a single anesthetic before the age of 4, and 3640 children had multiple anesthetics before age 4, and these exposed children were matched with 159,619 unexposed control children. The adjusted mean difference between a single exposure before age 4 and controls was 0.41% (95% confidence interval 0.12% to 0.70%) for poorer school grades and 0.97% (95% confidence interval 0.15% to 1.78%) for lower IQ scores. The magnitude of the difference remained the same for multiple exposures and there were no differences in school grades for the age of exposure (less than 6 months, 7-12 months, 13-24 months, or 25-36 months). The regression model found that the overall difference was markedly less than the differences associated with gender, maternal educational level, or month of birth.

**Exposure >4 years**

The Raine cohort from Australia included 2868 children born from 1989 to 1992 who were evaluated by a range of neuropsychologic tests. A study examining the neurodevelopmental outcomes after initial anesthetic exposure between the ages of 3 and 10 found that exposed and unexposed children had similar neuropsychologic tests except for the Neuromuscular Development motor function scores. Subgroup analysis found that children exposed between the ages of 3 and 5 (adjusted risk ratio: 2.32; 95% confidence interval, 1.42 to 3.79) and 5 and 10 years (adjusted risk ratio: 2.33; 95% confidence interval, 1.21 to 4.48) were at similarly higher risk for motor deficits compared with unexposed children.

An observational cohort was developed by linking public insurance claims from the states of Texas and New York from 1999 to 2010. Using common surgical procedures (circumcision, inguinal hernias, pyloromyotomy, tonsillectomy, and adenoidectomy) the timing of exposure from birth to age 5 was explored to determine whether there were higher rates of developmental delay or ADHD. A total of 38,493 children with a single exposure and 192,465 propensity score matched children unexposed before age 5 were included in the analysis. Increased risk of either developmental delay or ADHD was observed at all ages at exposure, with an overall hazard ratio of 1.26 (95% confidence interval 1.22 to 1.30), which did not vary significantly with the timing of exposure.

**Exposure during other sensitive periods of development**

Most concern about anesthetic induced developmental neurotoxicity has been focused on toddlers and infants because this is a time of critical development. For example, infants with strabismus between the ages of 3 and 8 months are unlikely to develop binocular vision, and thus this time period is a critical period during visual development. However, there may be other relevant times throughout the lifespan (fig 1). There are longer and important time periods such as between birth and 5 years when language is acquired. Adolescence is another developmental time of sensitivity and neurologic plasticity that deserves study, especially in light of reports linking anesthesia and surgery with ADHD.

**Mitigating the effects of anesthesia**

The first step of mitigation is to limit exposure whenever feasible. This does not mean avoiding general anesthesia and procedures in young children when the benefits of the procedures are clear.

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**Fig 1 |** The developing central nervous system has windows of critical period plasticity where specific sensor and cognitive domains are affected by environmental factors (adapted with permission from Hensch)
nor does it mean avoiding general anesthesia for procedures in young children with the premise that an unsedated or unanesthetized child undergoing a procedure is safer than a sedated or anesthetized child. It means measures should be taken to ensure that induction times are streamlined when possible and that care teams understand the goals of limiting both the duration of anesthetic exposure as well as limiting repeat exposures. Careful consideration should be given to delaying elective surgery until the child is older than 3 or 4 with the caveat that we still do not know what the most vulnerable period is for children. Further work is needed to determine whether certain anesthetic agents are less neurotoxic in both animals and humans and if so, feasible anesthetic strategies using less toxic agents should be developed.

Preclinical evidence shows that xenon gas (not a commercially available anesthetic) and dexmedetomidine may be less neurotoxic than other anesthetic agents. An ongoing international prospective randomized trial is comparing the neurocognitive outcomes at age 3 of infants who have undergone either an anesthetic with low dose sevoflurane/remifentanil/dexmedetomidine with standard dose sevoflurane for procedures lasting longer than two hours.99

The second step to mitigation is to reduce the negative impacts of neurotoxic exposure. Animal studies show that enriched environments may play an important role in reducing anesthetic harm.26 Other possible harmful effects of general anesthesia should be scrupulously avoided, such as hypotension, hypocarbia, hypoxia, hyperoxia, and hypoglycemia in all patients, but especially children.100 A multinational investigation has demonstrated the utility of intraoperative near infrared spectroscopy to monitor brain oxygenation in infants and children.101

New research
Two public-private partnerships are available to clinicians and families to learn about the latest recommendations and research in this field. Safetots (www.safetots.org) was established in Europe to emphasize the role of the conduct of anesthesia to prevent perioperative harm and to promote safe care. SmartTots (www.smarttots.org) was created to increase the safety of anesthetic drugs and sedative drugs for children undergoing general anesthesia and sedation. Both organizations are active in promoting research in these areas.

Additional work is needed to determine whether certain subgroups of children are at higher risk, in order to target them for mitigation. Identifying particularly vulnerable patients may lessen the potential morbidity that results from possible neurotoxicity and other adverse events, such as respiratory, cardiac, and hypoxic harm.100 102 A viable approach utilized in psychological research is to consider a “diathesis stress model,” which interrogates the complex interplay of the inherent vulnerability of the patient and the environment (fig 2).103 104 Vulnerable patients with severe comorbidities subjected to the stress of the perioperative period are more likely to have adverse outcomes.

Exploratory work has examined the relation between anesthetic cumulative dose and exposure duration and neurocognitive outcomes in a cohort of 217 long term survivors of childhood leukemia treated with chemotherapy alone. On average, these patients were cumulatively exposed to more than 15 hours of general anesthesia with more than 26 isolated exposures. Forty two per cent of the patients were deemed to have general neurocognitive impairments, with risk factors being total propofol dose, total isoflurane exposure, and total cumulative anesthetic duration.105 For

Fig 2 | The diathesis stress model serves as a paradigm that examines the interplay between genetic vulnerabilities of the patient (congenital lesions and prematurity) and stressful environmental factors (prolonged surgery, hospitalization, and anesthetic management)
vulnerable patients, genetic and environmental factors should therefore be identified and proactive measures to assure optimal homeostasis should guide clinical care.103

Guidelines
The FDA issued a warning in 2016 that repeated or prolonged use of general anesthesia in children younger than 3 might result in developmental problems in those children.108 The FDA also required warning labels on all anesthetic agents and sedatives from 2017. Many medical organizations in the US, spearheaded by the American Academy of Pediatrics, coordinated a response that endeavored to place the FDA warning into perspective and to reassure practitioners and the public that almost all studies show no developmental problems in children exposed to a single short anesthetic or sedation. Medical societies and regulatory agencies in other countries have declined to issue specific warnings about the safety of general anesthetic exposure in young children.

A consensus statement from the European Society of Anaesthesiology and other European medical societies in 2017 concluded that there was no compelling evidence to change anesthetic practice, but anesthesiologists should provide adequate information on the risks of avoiding a necessary intervention/anesthesia procedure as well as on the potential risks associated with anesthetic procedures.107 The statement also emphasized that a cut-off point of age 3 was not supported by evidence. A systematic review of neurocognitive assessment utilized in 67 clinical investigations in this area revealed a lack of consistency in cognitive domains, follow-up assessments, study populations, and age of exposure.108

Conclusions
The neurotoxic effect of anesthetic action has been demonstrated in the laboratory and most likely affects several signaling pathways.109 Although the FDA safety warning is alarming, it is based on preclinical data and findings in the neuroscience literature. The negative findings of the PANDA, MASK, and GAS studies suggest that the risk of anesthetic neurotoxicity in routine surgical procedures in early life is negligible if it exists at all. However, clinicians should acknowledge that these findings may be more complicated, and that further investigation is still needed.110

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RESEARCH QUESTIONS
• Given that reports of harm are limited to short anesthetics and surgery, are prolonged or repetitive exposures safe?
• At what age are children most vulnerable to general anesthetic neurotoxicity?
• Which children are at highest risk for general anesthetic neurotoxicity?


STATE OF THE ART REVIEW

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