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Anesthetic-related Neurotoxicity and Neuroimaging in Children: a Call for Conversation

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Abstract

Each year millions of young children undergo procedures requiring sedation or general anesthesia. An increasing proportion of these anesthetics are provided to optimize diagnostic imaging studies such as magnetic resonance imaging. Concern regarding the neurotoxicity of sedatives and anesthetics has prompted the US Food and Drug Administration to change labelling of anesthetics and sedative agents warning against repeated or prolonged exposure in young children. This review aims to summarize the risk of anesthesia in children with an emphasis on anesthetic-related neurotoxicity, acknowledge the value of pediatric neuroimaging, and address this call for conversation.

Keywords

anesthesia; anesthetic; children; diagnostic imaging; magnetic resonance imaging; neurodevelopment; neuroimaging; neurotoxicity; sedation

There is heightened concern surrounding the safety of sedation and anesthetic medications in young children. Animal studies consistently report brain injury and behavior changes in animals exposed to sedatives during critical periods of brain development. Likewise, evolving yet inconsistent human studies suggest an association between anesthetic exposure and cognitive delay. This theoretical risk of anesthetic-related neurotoxicity must be placed in the context of the known risks of procedural sedation and perceived benefits of the indicated procedure. SmartTots, a Public-Private Partnership between the US Food and Drug Administration (FDA) and the International Anesthesia Research Society, recently released a revised consensus statement recommending a conversation “among all members of the care team as well as the family” regarding timing of procedures or tests which require anesthesia

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while affirming that anesthetic drugs are a necessary part of diagnostic studies in infants and toddlers that cannot be delayed [1–3]. This statement is endorsed by 19 leading United States and global health organizations, including the American Academy of Pediatrics and the Society for Pediatric Anesthesia, and recommends that “concerns regarding the unknown risk of anesthetic exposure to [the] child’s brain development must be weighed against the potential harm associated with cancelling or delaying a needed procedure” [3]. More recently, the FDA announced the addition of a warning to be added to labels of general anesthetic and sedation medications indicating that “repeated and lengthy (>3 hours) use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women in the third trimester may affect the child’s developing brain” [4]. Neuroimaging is an increasingly common indication for sedation or general anesthesia in young children. Since child neurologists may be unfamiliar with the risks of general anesthesia/sedation and anesthesiologists may be unfamiliar with the clinical indications for neuroimaging, the authors aim to unite both specialties and review the risks of anesthesia and sedation in young children with an emphasis on anesthetic-related neurotoxicity, discuss the value of pediatric neuroimaging, and impart a framework from which this conversation might occur.

Risk of Anesthesia in Children

The safety of pediatric anesthesia has increased over the past several decades with improved monitoring, equipment, medications, and growing subspecialization and regionalization of pediatric care [5, 6]. Despite these advances, anesthetic-related complications occur more often in children compared to adults [7, 8]. Specifically, infants and children less than 3 years of age and children with comorbid conditions are at the highest risk of morbidity associated with general anesthesia [7, 9, 10]. Reasons for this increased anesthetic risk in young children are multifactorial and include limited cardiopulmonary reserve, multiorgan immaturity, altered total body water composition relative to adults, limited pharmacokinetic and pharmacodynamics data on commonly used medications in children, altered sensitivity to drugs relative to older children, temperature lability, care team experience, and monitoring difficulties, especially in magnetic resonance imaging (MRI) suites secondary to magnetic interference [11].

Anesthesia-related Neurotoxicity

Animal research reporting permanent neurocognitive impairment has created new concerns regarding the safety of anesthetics and sedatives in young children, generating significant attention and concern among health care providers and parents alike. Preclinical studies of anesthetic neurotoxicity originate from mechanistic studies of fetal alcohol syndrome, a well-known, well-characterized, permanent neurotoxic syndrome [12–16]. A sentinel study found that exposure of developing rodents to ethanol, a known *N*-methyl-D-aspartate (NMDA) receptor antagonist and γ -aminobutyric acid (GABA) receptor agonist, during periods of synaptogenesis caused widespread apoptotic neurodegeneration of the rat forebrain [14]. Since nearly all anesthetic and sedative agents are believed to modulate either NMDA- or GABA-mediated signaling, it was hypothesized that exposure of developing animals to common sedatives modulating these receptors might induce a similar degree of neuronal cell

death as that reported for ethanol. Over the last 15 years, there have been innumerable reports demonstrating widespread neurodegeneration in response to essentially all known sedatives and anesthetics with overt concern for long-term developmental impairment. These histologic changes have reported developmental significance as the combination of midazolam, nitrous oxide, and isoflurane induced both neuroapoptosis and persistent memory and learning impairments in infant rats [17]. These data has also been replicated in nonhuman primates, demonstrating both neuroapoptosis and persistent deficits in motivation, color and position discrimination tasks, response speed, and task performance accuracy after a single exposure to 24 hours of ketamine during the first week of life. Of note, these animals are presently over 5 years old and continue to demonstrate decreased task performance relative to controls [18]. A recent systematic review of preclinical anesthetic neurotoxicity studies in MEDLINE revealed close to 1,000 articles published since 2004 related to this subject [13]. Despite heterogeneous methodologies impairing direct comparison, preclinical studies suggest a window of vulnerability for anesthesia-induced neuronal cell death, the presence of a dose-dependent neurotoxic response to anesthetics, and amplified toxicity with multiple exposures to the same anesthetic agent [13, 19].

Replication of these animal studies in humans is not ethically possible, and direct translation of these results to clinical medicine is impossible. Thus, retrospective epidemiologic studies and emerging prospective clinical trials have been conducted or are currently underway to better understand the relevance of preclinical studies to young children, if any [20–26]. Despite known limitations of retrospective studies, heterogeneity in methodology, degree of confounding, and differing outcome measurements, a cumulative analysis suggests an association between adverse neurodevelopmental outcomes and exposure of anesthesia at an early age [12]. The strength of this association is weak, however, with the majority of studies reporting hazard ratios less than 2 [27, 28].

Despite their limitations, extant studies suggest that single brief anesthetic exposures do not appear to produce a measurable effect whereas repeated exposures consistently demonstrate associations between exposure and subsequent deficits in learning and behavior (Figure 1) [21]. The potential ramifications of the associations thus described emphasize the importance of the ongoing prospective studies to parents, providers, and regulators. The General Anesthesia Compared to Spinal Anesthesia (GAS) trial, an international multisite randomized controlled trial, was designed to study cognitive outcomes at 2 and 5 years of age in over 700 neonates randomized to either general or spinal anesthesia for hernia surgery [26]. Recent analysis of the secondary outcome (neurodevelopment at 2 years of age) found no evidence of adverse neurodevelopment at 2 years of age in infants receiving less than 1 hour of general anesthesia with sevoflurane compared with awake-regional anesthesia [26]. Similarly, the multicenter Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) study examined the effect of a single brief anesthetic on performance in a sibling cohort discordant for exposure to general anesthesia for inguinal hernia repair. Like the GAS study, the PANDA study examined the effect of a single brief exposure and was also negative [29–31]. In this multisite sibling-matched cohort study, healthy children exposed to a single anesthetic before 36 months of age compared to healthy siblings without anesthesia exposure had no difference in IQ scores in later childhood [31]. The Mayo Anesthesia

Safety in Kids (MASK) study is a collaboration between Mayo Clinic and the National Center for Toxicological Research (NCTR). [30] It is a population-based propensity-matched study comparing performance on neuropsychologic testing (NCTR-Operant Test Battery) of children who were exposed to anesthesia prior to 3 years of age with unexposed children. The Operant Test Battery has been used to study anesthetic-related neurotoxicity in nonhuman primates and offers a direct comparison of effects of anesthetic exposure in children and nonhuman primates performing identical behavioral tasks [30]. Human studies examining anesthesia and surgery associated neurodevelopmental outcomes are summarized in Table 1. Until further studies clarify the effect of anesthesia on neurodevelopmental outcome in young children, the risks remain unknown and health care teams are left to weigh the known risks (eg, aspiration, bronchospasm, laryngospasm, cardiac arrest) and unknown risks (eg, anesthetic-related neurotoxicity) of anesthesia with the perceived benefits of diagnostic procedures [3].

Sedation-related Neurotoxicity

As alluded to above, it is important to note that the label *anesthetic neurotoxicity* may be a misnomer because the implicated medications are widely used outside of the conduct of a general anesthetic. Equally important, subanesthetic doses of these sedatives demonstrate neurodegeneration in laboratory animals [39]. The same medications used during the course of a general anesthetic are commonly used for sedation for diagnostic and therapeutic procedures outside of the operating room. Exposure to these medications, particularly in the intensive care unit, may be of particular importance as doses are commonly high and exposure time prolonged [40–45].

Value of Neuroimaging in Children

Neuroimaging in infants and young children often requires sedation or general anesthesia for both patient comfort and accurate interpretation of study results. The value or diagnostic yield of imaging in children is a complicated discussion reflecting the heterogeneity of clinical indications. Most studies assessing imaging yield describe how often pertinent positive findings are identified that change acute management; however, the ability of imaging to rule out pathology is often equally important and its value understated. Diagnostic yield varies between organ systems, diagnoses within the same system, and even within the same general diagnosis. The pediatric neuroimaging guidelines set by the American Academy of Neurology depend on whether a child is being evaluated for microcephaly, status epilepticus, global developmental delay, or cerebral palsy [46]. A child presenting with classic clinical and electroencephalographic features of a genetic, generalized epilepsy and a normal examination does not necessarily need neuroimaging; whereas, neuroimaging is recommended in a child with focal epilepsy and an abnormal examination. The strength of evidence for neuroimaging varies by diagnosis. For instance, a substantial number of children with new-onset seizure and status epilepticus will have urgent or emergent intracranial pathology identified on neuroimaging while the vast majority of children with mild traumatic brain injury do not require neuroimaging [47, 48].

The risk-benefit analysis regarding imaging decision-making is complex. This includes decisions on the optimal imaging modality and optimal timing to obtain or repeat imaging. For example, an infant with hypoxic-ischemic encephalopathy may benefit more from a brain MRI compared to computed tomography (CT) study, but the imaging timing may depend on several factors, including concomitant therapeutic hypothermia [49]. While CT studies rarely require anesthesia in children, the diagnostic yield of a head CT can be limited and the risk associated with ionizing radiation in children is a major concern [50–52]. A retrospective study of pediatric CT scan use in the United Kingdom reported a dose-response relationship between risk of leukemia and brain cancer and ionizing radiation exposure – a dose-response relationship compatible with that observed in Japanese atomic bomb survivors [50, 53]. Re-analysis of the cohort excluding participants with cancer-predisposing conditions continued to show increased cancer risk after low-dose radiation exposure from CT scans in young children [53]. While the Joint Commission and the American College of Radiology promote the reduction of CT use in children, the long term impact of recent CT dose-reduction strategies on the risk of cancer in children is unknown [54]. Even though MRI does not expose children to radiation, risk exists apart from anesthesia as there is a strong association between gadolinium-based contrast agents used in MRI and nephrogenic system fibrosis (NSF) in patients with renal impairment and pro-inflammatory conditions [55]. While this multisystem disease is rare with ten biopsy-proven cases reported in children, it can be fatal [55].

Once a decision is made to pursue imaging, it is worth noting that options exist to help minimize risk. MRI-compatible neonatal incubators can help minimize transport-associated risk [56], and neonates can often tolerate a MRI while sleeping without the need for anesthesia. The frequency of unsedated MRIs in neonates is increasing, especially as MRI acquisition techniques advance to diminish movement artefact. [57] Ultra-fast techniques are available for some diagnostic studies, and evidence supports the use of ultra-fast MRI for the assessment of ventricular size in children with shunt-treated hydrocephalus. [57, 58] Finally, consideration may be given to combining multiple studies and procedures requiring anesthesia in children to limit exposure; however, an individual risk-benefit analysis in the context of the present healthcare practice may not support this as risk of transport and additional anesthesia exposure between studies may outweigh the perceived benefit.

Call for Conversation

When neuroimaging is necessary in young children, the prescribing physician is the ideal person to initiate a conversation with the family and care team regarding timing and outcome-changing potential of the requested study. Since most MRI studies in young children require sedation or general anesthesia, and sedation is no safer than general anesthesia, pediatric neurologists should be familiar with the risks in order to best navigate this discussion and address parental concerns, especially since parents are the ultimate patient advocate and consumer of mainstream media and are increasingly questioning the risk.

Since families differ in regard to the information desired, it is the authors' practice to take an individualized approach by discussing risks of anesthesia in general terms and inviting

parents and older children to ask for more specific information. Since the risk of anesthetic-related neurotoxicity is unknown and theoretical, no mention of this topic is made unless requested. Consistent with our practice, a recent survey of current pediatric anesthesia practices at United States teaching institutions found that over 90% of pediatric anesthesiologists discuss the issue of neurotoxicity “only if asked” [59]. When parents and older children do ask, the authors welcome the conversation and provide reassurance that a single, short exposure of general anesthesia does not appear to increase the risk of an adverse neurodevelopmental outcome [26, 31]. In addition, we share with inquisitive parents the low rate of harm associated with anesthesia and lack of compelling evidence to date of a causal relationship between anesthetic exposure and developmental delay. Since anesthesiologists often meet their patients on the day of the scheduled study when parents are anxious and children are fasting, child neurologists can help their colleagues in anesthesiology by preemptively addressing parental questions and affirming the importance of the recommended study to families, emphasizing how the test result will directly alter the child’s treatment plan and health outcome. Furthermore, pediatric anesthesiologists would willingly assist their colleagues in pediatric neurology with this discussion and welcome preprocedural consultation as questions and concerns arise.

Until further research clarifies the impact of anesthetic and sedative medications on neurodevelopment or until neuroimaging technology advances beyond the need for general anesthesia for these studies in young children, pediatric neurologists and anesthesiologists should work together engaging in conversation to provide the best care, minimizing risk and maximizing benefit for the health of all children [60].

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Flick et al[21]. Used with permission.

Figure 1.
Estimated cumulative percentage of children with learning disabilities (LD) for those with 0, 1, and multiple exposures to anesthesia before the age of 2 years[21].

Summary of Human Studies Examining Anesthesia and Surgery Associated Neurodevelopmental Outcomes

Table 1

	Design (study period)	Sample size	Operations	Age at exposure	Anesthetic agents and duration	Confounder adjustment	Outcome assessment	Follow-up	Neurodevelopmental outcomes
Adverse Neurodevelopmental Outcome									
DiMaggio et al. 2009[32]	Birth cohort (1999–2001)	383 exposed, 5050 unexposed	Inguinal hernia repair (ICD-9 code)	3 yrs	No	Age, sex, race, birth complications	4 yrs	Behavioral/Developmental ICD-9 codes	Increased incidence of behavioral/developmental diagnoses associated with hernia repair after controlling for confounders
Wilder et al. 2009[20]	Birth cohort (1976–1982)	449 singly exposed, 144 multiply exposed, and 4,674 unexposed	Varied	<4 yrs	Yes	Sex, birth weight, gestational age	19 yrs	LD cases identified based on research criteria from review of school and medical records	Two-fold increase in risk of LD frequency among multiple exposed children after adjustment
Bartels et al. 2009[33]	Twin-pair cohort (1986–1995)	154 exposed, 648 unexposed	Varied	<3 yrs and <12 yrs	No	Sex	12 yrs	Academic achievement and CTRS	Lower achievement scores in concordant twin pairs-exposed compared to concordant twin pairs-unexposed. No difference between twins within discordant twin pairs
DiMaggio et al. 2011[23]	Retrospective cohort (1999–2005)	304 exposed, 10,146 unexposed	Varied	<3 yrs	No	Sex, birth weight, birth-related complication, and clustering for sibling status; Sibling-matched analysis	4 yrs	Developmental and behavioral diagnoses (ICD-9 codes)	Increased risk of developmental and behavioral disorders among multiply exposed children. No difference in developmental or behavioral diagnoses among sibling pairs with discordant exposure status
Ing et al. 2012[25]	Birth cohort (1989–1992)	321 exposed, 2287 unexposed	Varied	<3 yrs	No	Sex, low birth weight, race, income, maternal education level	10 yrs	Neuropsychological test batteries	Impaired performance in language (CELF test) and cognition (CPM test), but not behavior or motor functions
Sprung et al. 2012[22]	Birth cohort (1976–1982)	286 singly exposed, 64	Varied	<2 yrs	Yes	Adjusted for sex, birth weight, and	19 yrs	ADHD cases identified based on research	Two-fold increase in risk of

	Design (study period)	Sample size	Operations	Age at exposure	Anesthetic agents and duration	Confounder adjustment	Outcome assessment	Follow-up	Neurodevelopmental outcomes
		multiple exposed, and 5,007 unexposed children				gestational age; stratified for propensity of receiving general anesthesia		criteria from review of school and medical records	ADHD frequency among multiply exposed children after adjustment
Flick et al. 2011[21]	Matched cohort (1976–1982)	286 single exposed, 64 multiple exposed, and 700 unexposed children	Varied	<2 yrs	Yes	Adjusted for sex, birth weight, and gestational age; Adjusted for propensity of receiving general anesthesia	19 yrs	LD cases identified based on research criteria, need for IEPs, and performance in group achievement tests	Two-fold increase in risk of LD frequency among multiply exposed children after adjustment. Increased need for IEP for speech language impairment
Block et al. 2012[34]	Cohort (1990–2008)	287 exposed	Inguinal hernia repair, orchidopexy, pyloromyotomy, and circumcision	<1 yr	Yes	CNS problems/risk factors, birth weight	7–10 yrs	Academic achievement tests	Association between lower test scores and longer duration of anesthesia and surgery. No difference in achievement test scores among children without CNS risk factors
Ing et al. 2014[35]	Birth cohort (1989–1992)	112 exposed, 669 unexposed	Varied	<3 yrs	No	Sex, low birth weight, race, income, and maternal education	10 yrs	Neuropsychological tests, ICD-9 codes, group-administered achievement tests	Compared with unexposed peers, exposed children had an increased risk of deficit in neuropsychological language assessments (CELF) and ICD-9 coded language and cognitive disorders, but not academic achievement scores
Stratmann et al. 2014[36]	Matched cohort (2011–2013)	28 exposed, 28 unexposed	Varied	<2 yrs	Yes	Age and sex matched; exclusion of intraoperative confounding factors	6–11 yrs	Test of recognition memory, IQ, and CBCL	Impairment in recollection memory in exposed children, but no difference in familiarity, IQ, or CBCL
Backeljauw et al. 2015[37]	Matched cohort (Recent)	53 exposed, 53 unexposed	Varied	<4 yrs	Yes	Age, sex, handedness, SES	5–18 yrs	OWLS and WAIS or WISC	Lower score in listening comprehension and performance IQ among

	Design (study period)	Sample size	Operations	Age at exposure	Anesthetic agents and duration	Confounder adjustment	Outcome assessment	Follow-up	Neurodevelopmental outcomes
No Difference in Neurodevelopmental Outcome									
Hansen et al. 2011[24]	Birth cohort (1986–1990)	2,689 exposed, 14,575 unexposed	Inguinal hernia repair	<1 yr	No	Sex, birth weight, parental age and education	15–16 yrs	Ninth grade test average and average teacher rating	No significant difference in test performance.
Hansen et al. 2013[38]	Birth cohort (1986–1990)	779 exposed, 14,665 unexposed	Pyloromyotomy	<3 mo	No	Sex, birth weight, parental age and education	15–16 yrs	Ninth grade test average and average teacher rating	No significant difference in test performance.
Davidson et al. 2016[26]	Randomized controlled trial (2007–2013)	238 RA, 294 GA	Inguinal herniorrhaphy	Up to 60 weeks post-menstrual age	Yes	No (randomized trial)	2 yrs	Neuropsychological test batteries (Bayley-III and MacArthur-Bates scores)	No difference in Bayley-III and MacArthur-Bates scores at 2 yrs
Sun et al. 2016[31]	Sibling matched cohort	105 sibling pairs	Inguinal herniorrhaphy	<3 yrs	Yes	Sibling matched, age difference within 3 yrs	8–15 yrs	Neuropsychological test batteries	No statistically significant differences in mean scores between sibling pairs in IQ, memory/learning, motor/processing speed, visuospatial function, attention, executive function, language, or behavior.

Abbreviations: ADHD, attention deficit hyperactivity disorder; CBCL, Achenbach Child Behavior Checklist; CELF, clinical evaluation of language fundamentals; CNS, central nervous system; CPM, Raven's Colored Progressive Matrices; CTRS, Connor Teacher Rating Scale; GA, general anesthesia; ICD-9, *International Classification of Diseases*; Ninth Revision; IEP, individualized education program; IQ, intelligence quotient; LD, learning disabilities; OWLS, Oral and Written Language Scales; RA, regional anesthesia; SES, socioeconomic status; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children.

Table 2

Frequency of Perioperative Cardiac Arrests by Age

Table 2. Frequency of Perioperative Cardiac Arrests by Age

Age	Overall				Noncardiac Surgery/Procedure				Cardiac Surgery			
	CAs per 10,000 Anesthetics				CAs per 10,000 Anesthetics				CAs per 10,000 Anesthetics			
	Anesthetics, n	CAs,* n	Estimate	95% CI	Anesthetics, n	CAs,* n	Estimate	95% CI	Anesthetics, n	CAs,* n	Estimate	95% CI
0 to 30 days	1,451	23	158.5	100.7–236.9	1,014	4	39.4	10.8–100.7	437	19	434.8	263.8–670.7
31 days to 1 yr	7,807	18	23.1	13.7–36.4	7,045	3	4.3	0.9–12.4	762	15	196.9	110.6–322.6
Overall < 1 yr	9,258	41	44.3	31.8–60.0	8,059	7	8.7	3.5–17.9	1,199	34	283.6	197.2–394.0
1 to 3 yr	19,205	15	7.8	4.4–12.9	18,354	5	2.7	0.9–6.4	851	10	117.5	56.5–215.0
4 to 9 yr	25,650	11	4.3	2.1–7.7	24,510	7	2.9	1.1–5.9	1,140	4	35.1	9.6–89.6
10 to < 18 yr	38,768	13	3.4	1.8–5.7	37,716	7	1.9	0.7–3.8	1,052	6	57.0	21.0–123.7
Total, 0 days to < 18 yr	92,881	80	8.6	6.8–10.7	88,639	26	2.9	1.9–4.3	4,242	54	127.3	95.8–165.8
		43*	4.6*	3.4–6.2*						17*	40.1*	23.4–64.1*

* Estimates after "inability to wean from cardiopulmonary bypass" were excluded. Italicized data represent overall incidence of cardiac arrests (CAs) for infants (overall < 1 yr) and for the entire pediatric population (total).

CI = confidence interval.

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* Estimates after "Inability to wean from cardiopulmonary bypass" were excluded. Italicized data represent overall incidence of cardiac arrests (CAs) for infants (overall < 1 yr) and for the entire pediatric population (total).

CI = confidence interval.