**AANA Journal Course**

**Update for Nurse Anesthetists**

*Anesthesia and the Developing Brain*

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Despite the profound evolution in the safety and efficacy of neonatal and pediatric anesthesia, questions remain concerning the long-term neurotoxic and neurocognitive effects of the drugs used in anesthetic care. A variety of prospective animal models and retrospective human studies exist that inconsistently demonstrate a detrimental effect of early life exposure to anesthetic drugs and subsequent learning performance. Limitations associated with both non-human and human observational studies are critiqued. Research currently underway is briefly described. A framework for discussing the relevant issues with concerned parents is presented.

**Keywords:** Apoptosis, neurocognitive effect of anesthetic drugs, neurotoxicity of anesthetic drugs, pediatric anesthesia.

**Objectives**

At the completion of this course, the reader should be able to:

1. Discuss the historical evolution of pediatric anesthesia relative to the physiology of pain interpretation of the very young.
2. Describe the role of normal and accelerated apoptosis in the developing brain.
3. Describe the limitations of prospective animal research and retrospective human research focusing on the anesthetic effects of subsequent neurocognition.
4. Describe an understanding of the proposed mechanism of action of inhalation anesthetics and sedatives in the role of apoptosis.
5. Identify how to address parental concerns regarding the anesthetic management of their child.

**Introduction**

Over the last 3 decades, the delivery of anesthetic care to the young child has undergone a revolution of thought and practice. In the early 1980s, the administration of general anesthesia to the most vulnerable newborns and infants was avoided, as it was believed to incur significant cardiovascular and respiratory risk. Ductus arteriosus ligations were often performed in the neonate without the benefit of hypnosis and analgesia, using a blend of oxygen, nitrous oxide, and skeletal muscle relaxation. It was believed that the neonate had an immature nociceptive system, did not experience pain, was unable to mount a neuroendocrine stress response to a surgical procedure, and could not retain long-term memory of painful events.

Subsequent clinical investigations discredited these long-held beliefs, demonstrating that introduction of a painful stimulus in the neonate resulted in profound metabolic and endocrine responses in the absence of adequate anesthesia and analgesia. Providing an appropiate depth of anesthesia was also essential in preventing exaggerated neuroendocrine responses. Given these insights, and the development of newer anesthetic agents associated with less myocardial depression, the anesthetic standard of care of the very young now mirrors that of the adult, emphasizing the importance of providing hypnosis, amnesia, analgesia, and the blunting of the surgical stress response.

In the last 15 years, a large body of literature using animal models and retrospective human studies has been published. Most of these investigations demonstrate a detrimental effect of early life exposure to anesthetic drugs on subsequent learning performance. The number of laboratory investigations confirming these findings in a diversity of animals (mouse, rat, rhesus monkey, and others) is disquieting (Table 1). Histologic evidence of neuronal degeneration may not be restricted to the...
neurons, as a recent study in a primate model found that anesthetic exposure resulted in degeneration of oligodendrocytes as well. The concern that contemporary anesthetic agents may produce potentially harmful neurological effects in the immature human emerged as one of the most urgent issues in pediatric anesthesia. In the wake of a growing body of literature, agencies such as the Food and Drug Administration (FDA) and the International Anesthesia Research Society have organized meetings of researchers and practitioners, and encouraged fundraising to promote research examining the safe use of contemporary anesthetics in neonates, infants, and children.

The Role of Neuronal Apoptosis and the Developing Brain

For a complete treatise on apoptosis, the reader is referred to the comprehensive review by Bennetts and Pierce. In brief, apoptosis is an energy-dependent physiological process of programmed cell death that functions to remove injured or duplicate cells in balance with the continuous mitotic production of new cells. This energy-dependent process is a keenly regulated biochemical process directed by the caspase enzyme system, resulting in fragmentation of targeted cells into discrete elements that are ultimately phagocytized by macrophages and neighboring cells. Unlike necrosis—an energy-independent process initiated by pathological cell insult—neighboring cells are not injured during apoptosis.

The mammalian brain undergoes a rapid growth spurt during the last trimester of gestation until the 3rd year of life. This period of neurogenesis/synaptogenesis results in the production of superfluous neurons and neurons with erroneous synaptic connections that are eventually removed by apoptosis and synaptic regression. Neuronal and synaptic loss is not uniform throughout the brain and is regulated by a complex process that involves genetics, neuronal age, and maturation. The initial period of apoptosis targets progenitor cells and occurs in early embryonic development while a second period of apoptosis targets postmitotic neurons. Neural apoptosis results in the loss of up 50%–70% of the existing neurons and synaptic connections. This process is essential for normal brain development and structure. Failure of apoptosis during the final trimester leads to brain malformation and intrauterine death.

What Is the Evidence for Anesthetic-induced Neuroapoptosis?

Although the precise mechanistic action of inhalation anesthetics, sedatives, and anticonvulsants remains incompletely elucidated, the observed effects are largely reasoned to be the result of neuronal activity via the antagonism of glutamate N-methyl-D-aspartate (NMDA) receptors and activation of γ-aminobutyric acid (GABA_\alpha) receptors (Table 2).

NMDA and GABA receptor activity are essential for normal neural development. The NMDA receptor is an essential fundamental excitatory transmitter, playing a crucial role in the complex processes of learning and memory formation. NMDA receptor activation produces an opening of an ion channel, resulting in the influx of sodium and calcium and the efflux of potassium ions. The influx of calcium through this ion channel is essential for synaptic structure, connectivity, and long-term synaptic strength.

The GABA receptor is an ionotropic receptor and ligand-gated ion channel (Figure 1). The GABA receptor is inhibitory in the adult brain, acting to lower metabolic rate. During brain development in the rodent, GABA is excitatory in character. GABA excitation results in the transportation of chloride into the neuron via a sodium-, potassium-, and chloride-transporter producing cell hyperpolarization, thus inhibiting neurotransmission. GABA receptor excitation is essential for synaptogenesis. GABA receptors in the rat remain excitatory until approximately the 15th postnatal week, when they begin to transform into an inhibitory receptor with the maturation of chloride transporter, moving chloride out of the neuron. This transformation is not complete until the end of the first year of life.

In 1999 Ikonomidou, examining the effects of fetal ethanol exposure, reported a triggering of dual mechanistic (NMDA antagonist and GABA agonist) apoptotic neuronal degeneration throughout the rat forebrain during the period of rapid brain growth. This finding has major implications, as a number of pharmacological agents have mechanisms of action grounded in both NMDA and GABA receptor function. However, it was the landmark study by Jevtovic-Todorovic et al that generated a sense of urgency in the pediatric anesthetic community. Their 6-hour exposure of 7-day-old rats to commonly used drugs (combination of nitrous oxide, an NMDA antagonist, and the GABA agonists midazolam and isoflurane), produced widespread apoptotic neurodegeneration within the hippocampus, resulting in persistent deficits

Table 1. Observed Effects of Contemporary Anesthetics and Sedatives on Neuro Development in Immature Animals and Non-Human Primates

<table>
<thead>
<tr>
<th>Effects</th>
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<tbody>
<tr>
<td>Acute neuronal cell death</td>
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<tr>
<td>Neuronal cell disruption</td>
</tr>
<tr>
<td>Alterations in dendritic architecture</td>
</tr>
<tr>
<td>Decreased synaptic density</td>
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<tr>
<td>Mitochondrial deterioration</td>
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<tr>
<td>Decreased in neurotrophic factors</td>
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<tr>
<td>Impaired long-term cognitive, function</td>
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</table>

Immature animals include chicks, mice, rats, guinea pigs, pigs, and rhesus monkeys.
in learning and memory (see Table 1). Their observations suggested that profound apoptotic neurodegeneration was more widespread when both NMDA and GABA receptor function was altered (dual mechanistic action as in fetal ethanol exposure) than when either NMDA antagonists or GABA agonists were administered alone.

**Research in Animals**

We will only briefly examine work involving animal models because the application to humans remains speculative. There is always great risk and uncertainty when attempting to apply findings observed in one species to another. For example, anesthetic management in laboratory animals is not comparable to contemporary anesthetic practice with regard to hemodynamic monitoring, and airway and ventilator management. Hypoxia, hypercarbia, and the accompanying acidosis as well as hypoglycemia that would be well tolerated in the laboratory setting would be aggressively treated in the anesthetic management of the human patient. Experimental animals are typically not exposed to pain and the accompanying stresses of a surgical procedure.

The plasma concentrations of intravenous agents to generate neuronal degeneration are often 10x greater than those in humans. Additionally, the brain growth spurt of a rodent is considerably shorter (days) compared to years in the human.

If we only consider research performed in young primates—arguably the closest models in genetics and physiology to humans—there is good evidence that the currently used inhaled anesthetics result in neurodegenerative processes at doses and durations comparable to that seen in everyday practice. Apoptosis appears to occur with the greatest propensity in the cortical regions of the brain. These regions are associated with aspects of an animal’s behavior involving learning and attentiveness to their surroundings. Animal evidence indicates that early exposure to anesthetic agents, sedatives, and anticonvulsants during the rapid brain growth spurt may accelerate apoptosis, resulting in long-term cognitive and behavioral impairment. In these studies, dose and duration were not always controlled to mirror human application. Furthermore, we argue that virtually any substance—even oxygen or water—will exert neurotoxic

**Figure 1. The GABA Receptor**

<table>
<thead>
<tr>
<th>Agent</th>
<th>NMDA receptor antagonist</th>
<th>GABA&lt;sub&gt;b&lt;/sub&gt; receptor agonist</th>
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</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ketamine</td>
<td>+</td>
<td></td>
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<tr>
<td>Nitrous oxide</td>
<td>+</td>
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<tr>
<td>Inhalation anesthetics</td>
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<td>+</td>
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<td>Propofol</td>
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<td>+</td>
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<tr>
<td>Barbiturates</td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Phenytoin</td>
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*Table 2. Mechanistic Actions of Anesthetics, Sedatives, and Anticonvulsants*

*Although other mechanisms of action may be involved, these actions have been systematically demonstrated and defined.*
effect when applied under certain experimental conditions that may not reflect their defined clinical use.

Human Studies
This is a selective discussion and therefore not a complete review of all available human studies. For a complete treatise, the reader is referred to the excellent review by Loepke and Soriano.20 Studies involving young humans are fraught with logistical, methodological, and ethical hazards that are nearly without peer in terms of the complexities involved. In an effort to circumvent many of these issues, investigators to date have employed existing databases of anesthesia care from a single healthcare facility or a select geographic area, and then link them with subsequent measures, such as scholastic performance, in an effort to seek potential associations (Figure 2). It should be emphasized that these databases were preexisting (retrospective) and not prospectively developed to examine neurodevelopmental outcomes following general anesthesia.

An example of this is a recent study involving 5,357 children living in Olmsted County Minnesota, identified retrospectively, who underwent general anesthesia during the first 4 years of life.21 These children were subsequently assessed in terms of learning disabilities using several measures. The authors found that a single anesthetic was not associated with later development of a learning disability but did observe such an association with multiple anesthetic exposures. Many of these children did not have continuous pulse oximetry monitoring and received halothane (a now obsolete agent in the US), questioning the applicability of these findings to contemporary pediatric anesthesia practice.

In a study performed in children undergoing circumcision, orchiopexy, hernia repair, or pyloromyotomy at the University of Iowa, archived medical records were matched with later academic achievement testing.22 These surgeries were selected because they are frequently performed in well children. A greater-than-expected number of children without risk factors for central nervous system problems during infancy showed very poor test performance relative to population norms. Longer durations of anesthesia exposure were associated with poorer test scores. The authors noted that they were unable to differentiate the effects of the surgery itself from those of the anesthetic agents, or the combination of anesthesia and surgery.

In a re-analysis of the previously mentioned Minnesota data set, Mayo Clinic researchers examined attention deficit hyperactivity disorder (ADHD) as a surrogate measure for the toxic effects of anesthetics in the very young.23 The researchers set out to examine the association between exposures to general anesthesia prior to age 2 and the occurrence of subsequently diagnosed ADHD. Their analysis revealed that multiple general anesthetics were associated with an increased incidence of a subsequent diagnosis of ADHD. No association was found for children who underwent only 1 general anesthetic, even when comorbidities were considered.

Studies using data from outside the United States reveal a similar trend. A recent report using an Australian database, also retrospective, found that even a single general anesthetic prior to age 3 was found to be strongly associated with subsequent language and cognitive deficits in children.24 Concern about the foregoing findings should be tempered; not all clinical research has observed learning deficits in children who have undergone general anesthesia. For example, a study from Denmark examined children who underwent herniorrhaphy with an age-matched sample and found little evidence of an association with subsequent academic performance.25 A study conducted in the Netherlands involving 1,143 twin pairs found little evidence of a causative influence of early anesthetic exposure on subsequent academic achievement or cognitive problems.26 It is essential to appreciate several things as we consider the above studies. First, all were retrospective, and thus control of confounding factors (eg, intraoperative management, nutrition, medical care of comorbidity) did not occur. Second, the effects of inflammation on the central nervous system, as well as on other systems, is only beginning to be explored.27 What role it may have in the postoperative brain function of neonates, as it likely has in the aged patient, remains to be elucidated. Finally, we must critically consider if the need for anesthesia is simply serving as a marker for other as yet unidentified factors that lead to learning disabilities.

Is Anesthetic Management a Threat to the Developing Brain?
Neonates, infants, and children may require sedation or general anesthesia for diagnosis or the surgical correction of a variety of congenital disorders (Table 3). Neonatal organ system immaturity increases the risk of physiological perturbations during general anesthesia. Potential influences on subsequent neurotoxicity or neurocognitive impairment may include genetics, nutrition, intraoperative hypotension, hypoxia, hypocapnia, blood glucose levels, core temperature, percentage of oxygen used, the stress of the hospitalization, skill of the anesthesia provider, and known and unknown comorbidities. Here, we briefly consider the potential influences of altered intraoperative hemodynamics.

Perioperative alterations in blood pressure may alter cerebral perfusion and precipitate neurological injury.28 Hypotension following anesthetic induction is common. A recent review of over 22,000 anesthesia records found that nearly one-third of children aged 1–5 who underwent noncardiac surgery developed clinically significant hypotension prior to surgical incision.29 However, there
is a lack of literature demonstrating neurological injury following these hypotensive episodes.

Blood pressure often serves as a surrogate determinant of organ perfusion. However, assuming that higher systemic blood pressure and afterload in a sick neonate with limited cardiac reserve unequivocally results in a higher cardiac output may be specious. The safe lower limits of blood pressure and the resultant effects upon cerebral perfusion in the neonate are unknown. What anesthesia providers should define as hypotension in the neonate is also unsettled. A guideline widely maintained and practiced in the neonatal intensive care unit is that the adequate minimum value of mean arterial blood pressure should be equal to the neonate’s gestational age in weeks. This could result in a blood pressure dangerously close to the poorly defined lower limit of cerebral perfusion. A survey of registered members of the Society of Pediatric Anesthesiologists (SPA) and the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA) found that nearly three-fourths of respondents relied upon either mean arterial or systolic pressure in defining hypotension and identified a threshold of 45–50 mm Hg or a 20%–30% decrease from baseline blood pressure as hypotension in children during anesthesia. Are these thresholds adequate to ensure cerebral perfusion?

To optimally determine the influences of anesthetics and sedatives upon altered neurodevelopmental outcome, there should be clinical strategies to define what constitutes the safe clinical anesthetic management of anesthesia in the neonate, infant, and child. An examination of intraoperative vital signs, fluid administration, intra- and postoperative pain management strategies, and a detailed accounting of complications related to the care provided should attend such studies. As Weiss et al echoed in a recent editorial, why have we held our tools (anesthetics agents) responsible for altered neurodevelopmental outcomes without a critical examination of the influences of anesthetic management? In addition, the application of newer technologies, such as near-infrared spectroscopy.

Table 3. Common Surgical Procedures Requiring Anesthesia and Sedation

<table>
<thead>
<tr>
<th>Ophthalmology</th>
<th>Laser therapy</th>
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<tbody>
<tr>
<td>General surgery</td>
<td>Tracheoesophageal fistula</td>
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<tr>
<td></td>
<td>Congenital diaphragmatic hernia</td>
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<tr>
<td></td>
<td>Pyloromyotomy</td>
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<td></td>
<td>Laparotomy for prostatic obstruction</td>
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<tr>
<td></td>
<td>Hirschsprung disease</td>
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<tr>
<td>Gastrointestinal</td>
<td>Central venous access</td>
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<tr>
<td></td>
<td>Inguinal hernia</td>
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<tr>
<td></td>
<td>Imperforate anus</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Myelomeningocele</td>
</tr>
<tr>
<td></td>
<td>Encephalocoele</td>
</tr>
<tr>
<td></td>
<td>Ventriculoperitoneal shunt</td>
</tr>
<tr>
<td>Plastic surgery</td>
<td>Cleft palate/lip</td>
</tr>
<tr>
<td>Radiology</td>
<td>Cardiac catheter for diagnosis</td>
</tr>
<tr>
<td></td>
<td>Cardiac catheter for atrial septostomy, pulmonary artery stenting</td>
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<tr>
<td></td>
<td>Magnetic resonance imaging</td>
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<td>Computed tomography</td>
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<tr>
<td>Urological surgery</td>
<td>Cystoscopy</td>
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<tr>
<td></td>
<td>Hypospadiats</td>
</tr>
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<td></td>
<td>Reimplantation of ureters</td>
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</tbody>
</table>

Figure 2. Unravelling the Anesthetic Effects on the Developing Brain

Current studies in humans rely on existing databases. Logistic and ethical issues render prospective studies very complex.
copy to determine cerebral oxygenation, may assist the
determination of acceptable systemic blood pressure in
healthy, as well as critically ill, newborns and infants.

The Need for Caution and a Look to What Is
Coming Next

The fundamental question to those who provide pediat-
ric anesthesia services, and that which is of concern to
parents is: Does administration of general anesthesia at an
early age in human development lead to neurocognitive com-
plications? The power of the observational (nonrandom-
ized, incompletely controlled) study in other contexts is
well known. Think of what we have learned from obser-
vational methods in terms of the effects of smoking and
lung cancer, of sudden infant death syndrome and sleep
position, of diabetes and nutrition, and countless other
relationships that would be impossible to elucidate solely
with the methodology of the randomized controlled trial
(RCT). In the manner of science that demands causa-
tion as the endpoint, the RCT seems most appropriate,
though the logistics of such an undertaking is substantial
in terms of time, expense, personnel, and ethical issues.

The Hill Criteria

In the early 1960s, Sir Austin Bradford Hill, a pioneering
physician epidemiologist based in London, and a pioneer
in the development of the RCT, struggled with the ques-
tion of when to translate observational data as inferring
causation. Hill proposed a set of criteria that he believed
necessitated strict consideration, before one could con-
side the use of epidemiologic (observational) studies to infer causation.35,36 These criteria are referred to as
“Hill’s Criteria of Causation” (Table 4). Hill’s causative
criteria, to this day, remain foundational to the science
of epidemiology, and merit careful consideration when
assessing any observational or retrospective study for its
potential for causal inference.

Citing the profound and well-appreciated associations of
crotal cancer and chimney sweeps, salicylate use and
Reye’s syndrome in children, and smoking and lung
cancer, Hill argued that there were powerful observations
that defied, for logistical and ethical reasons, the oppor-
tunity to be tested with a randomized trial. Hill reasoned
that if his criteria were met, then certain associations,
established by observational studies, could be advanced
as causative.

What then would Hill allow us to conclude at this
juncture in the science of the neurotoxicity of anesthetic
agents in the very young? Perhaps this and no more: studies cannot exclude the possibility that the anesthetic
drug-induced neurotoxicity seen in some animal models may
also occur in children.

Prospective Research Currently Underway

In an effort to seek systematically derived evidence that
better defines any extant cause-and-effect relationships,
a number of prospective trials are currently underway. These
will be briefly reviewed.

1. Strategies for Mitigating Anesthesia-Related neuro-
Toxicity in Tots (Smart Tots)
The SmartTots initiative will fund research focused
primarily on 3 fundamental question domains:

- What is the spectrum of general anesthetic agents,
sedatives, surgical procedures, and/or opiates that
cause developmental neurotoxicity? What are the
doses, durations, and frequencies of exposure? What
are the most vulnerable periods of development?
- Are there short- and long-term neurocognitive,
emotional, behavioral, and/or social outcomes
resulting from exposure to anesthetic agents?
- What approaches can be taken to prevent or miti-
gate developmental anesthetic neurotoxicity?

2. The Effects of Anaesthesia on Neurodevelopmental
Outcome and Apnoea in Infants

This prospective RCT aims to compare neurodevelop-
ment following general and regional anesthesia in infants
undergoing inguinal hernia repair. The study has re-
 cruited more than 700 infants in 7 different countries, in-
cluding the United States. Neurocognitive-developmental
testing will take place at the child’s age of 2 years (2014)
and again at the age of 5 years (2016), with the final
results not available until 2017. This study will also
provide much-needed outcomes data related to the fre-
cuency of apnea in the immediate postoperative period.

3. The Pediatric Anesthesia and Neurodevelopment
Assessment (PANDA) Study

This is a multisite study that is currently underway
and uses a sibling-matched sample. Exposed siblings
(American Society of Anesthesiologist Classification I
or II) received a single anesthetic for inguinal hernior-
rhaphy prior to the age of 36 months, while the unex-
posed sibling received no anesthesia prior to the age of
36 months. Prospective neuropsychological assessment
will be performed in both the exposed and unexposed
siblings at ages 8 and 11 years old.

4. The General Anesthesia During Human Infancy and
Brain Development Study

This University of Iowa study is comparing children
aged 12–15 years who were or were not exposed to
general anesthesia and surgery during infancy, using
measures of brain tissue volume and composition and
white matter integrity (structural MRI), memory-related
regional brain activation during long-term and working
memory tests and resting-state functional connectivity
(functional MRI), and cognitive test performance. To
the best of our knowledge, no imaging studies have been
published to date that directly assess possible effects on
brain structure or function of general anesthesia and
surgery in infants without other major risk factors for
central nervous system disorders.
No matter what information emerges from previous and ongoing prospective studies, understanding neurocognitive development in children following anesthesia and surgery is an enormously complex undertaking and any emerging associations are likely to involve many factors (Figure 3). It is scientifically and clinically myopic to focus our efforts exclusively on the neurotoxicity of anesthesia. The influences of pain, inflammation, stress, comorbidities, and genetics may be complexly and inextricably wedded to the child’s outcome.

How to Handle Parental Questions

Over 1 million children under the age of 4 years undergo vital surgical and diagnostic procedures annually. The postponement of a necessary diagnostic or surgical procedure may result in significant additional health problems for the child. In the authors’ experience, the typical concerns verbalized by parents during the preoperative discussions of anesthetic risk include sore throat, postoperative nausea and vomiting, the treatment of anticipated postoperative pain, and how soon they will see the child following the surgical procedure. How does the anesthesia provider approach the parent who has asked if the administration of general anesthetics or sedatives for a diagnostic or surgical procedure might be harmful to their child’s neurocognitive development?

As we previously discussed, there is risk and uncertainty when attempting to apply findings observed in animals to humans. The parent may be conversant with animal evidence conveyed through mass media or internet sources that sedative and inhaled anesthetics currently in use may result in neurodegenerative processes in animals. Those parents are seldom fully conversant with the science, and frequently confuse association with causation. How then can we address their concerns?

SmartTots, in cooperation with the International Anesthesia Research Society, has released a consensus statement on the use of anesthetics and sedations in children. This statement encourages healthcare providers to engage parents and:

- 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.
- Recognize that current anesthetics and sedatives are necessary for infants and children who require surgery or other painful and stressful procedures.

As discussed earlier, providing amnesia and analgesia is essential in preventing the development of hyperalge-
sia, altered central nervous system development, and the blunting of neuroendocrine responses. Overly creative anesthetic plans that attempt to “minimize an unknown and as yet undefined risk” may lead to unintended adverse neurocognitive outcome. Currently, there is a lack of human data unequivocally implicating anesthetic drugs and sedatives in subsequent altered neurocognitive development.

Conclusion
The concern that contemporary anesthetic agents may produce harmful neurological effects in the immature human neonate and the young child has emerged as one of the most urgent issues in pediatric anesthesia. Animal evidence indicates that early exposure to anesthetic agents, sedatives, and anticonvulsants during the rapid brain growth spurt may accelerate apoptosis, resulting in long-term cognitive and behavioral impairment. Although research is currently focused on possible effects of early exposure to these drugs on neurocognitive development in humans, outcome may also be influenced by a host of factors including nutrition, environment (nurture), pain, inflammation, perioperative stress, comorbidities, and genetics.

A recent study indicated that the divergent findings in previous studies of post-surgical/anesthetic neurocognitive deficits may be significantly influenced by the outcome measures employed. This should serve as a cautionary note to those involved in ongoing prospective trials.

REFERENCES


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**DISCLOSURES**

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