Anesthesia is generally accepted as safe in most adult populations; however, in pediatric patients questions exist regarding the potential for long-term detrimental effects. Various anesthetic agents are associated with neuronal degeneration when administered to neonatal animals. The mechanism of damage is thought to be via accelerated apoptosis, a normally beneficial process in the maintenance of homeostasis. This review of the literature examines the current evidence in neonatal rodents, nonhuman primates, and humans experiencing anesthesia-induced neuronal apoptosis. Included are studies published between the years 2000 and 2010. Much of the early research subjects were rodents, with more recent studies examining nonhuman primates. Retrospective research of human populations is included as well, some of which is currently underway. Clear evidence exists that neuronal apoptosis occurs when anesthetics are administered to neonatal rodents and primates, and behavioral and cognitive testing from some authors indicate long-term effects persist well into an animal’s adulthood. Preliminary human trials reveal a link between anesthesia and subsequent developmental delays. This review of the literature clarifies the need for further research in humans.

**Keywords:** Anesthesia, apoptosis, neonate, neuronal apoptosis, neurodegeneration.

The concept of “do no harm” permeates healthcare doctrine worldwide, and in no field is this more crucial than in pediatric anesthesia. Pediatric patients are a particularly vulnerable population, and with close to 3 million children in the United States undergoing anesthesia annually, according to the 2004 National Hospital Discharge Survey.1 Therefore, the prudent anesthesia provider should be aware of potential implications of the agents administered. In recent years multiple studies have illustrated a link between various anesthetic agents and neuronal damage in neonatal animals. This research has brought to the forefront the notion of safety when administering anesthetics to pediatric patients. The question remains, however, whether these studies are applicable to humans.

This review discusses the significance and timeliness of the question of anesthetic-induced neuronal apoptosis in humans. In recent years, numerous studies have been conducted with the aim of clarifying the issue. The findings of the research as a whole demonstrate 3 key points: (1) N-methyl-d-aspartate (NMDA) antagonists and GABAergic agents consistently produce dose-dependent neuronal apoptosis in rodents, (2) these agents may produce apoptosis in nonhuman primates, and (3) limited human studies with anesthetics have produced variable results.

Agents most frequently analyzed include ketamine, isoflurane, and propofol, all of which bear clinical relevance to human pediatric anesthesia practice. The apoptotic effects of these agents appear to be dose-dependent, with multiple studies finding increased levels of neuronal apoptosis with increased drug dosage or exposure duration. The dose-dependent nature of anesthetic-induced neuronal apoptosis is confirmed by 2 human-based retrospective studies.2,3

Dosing of anesthetic agents in much of the animal research is quite high, approaching toxicologic levels in many cases if applied to human subjects. Researchers have determined, however, that the effective dose in small animals for most agents is significantly higher than in humans.4-7

In addition to dose-dependency, anesthetic-induced neuronal apoptosis appears to increase dramatically when combinations of drugs are administered.1,8 In their landmark study, Jevtovic-Todorovic et al8 saw profound, widespread apoptosis in rodents exposed to a clinically relevant combination of midazolam, isoflurane, and nitrous oxide. These researchers, as well as Fredriksson et al,9 found significant neurobehavioral and cognitive delays in rodents receiving a combination treatment when compared to controls.

Current pediatric anesthesia practice frequently involves the utilization of a variety of sedative and anesthetic agents. Many of these act as agonists at the γ-aminobutyric acid (GABA) receptor's alpha subunit, or as NMDA antagonists. Most anesthetic agents affect one or both of these receptor sites, including barbiturates, benzodiazepines, propofol, ketamine, nitrous oxide, and...
<table>
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<tr>
<th>Authors (y)</th>
<th>Sample type and size</th>
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<td>Cattano et al, 2008&lt;sup&gt;4&lt;/sup&gt;</td>
<td>P5-7 mice</td>
<td>Experiment 1: Determination of minimum propofol dose required to induce anesthesia</td>
<td>Propofol ED&lt;sub&gt;50&lt;/sub&gt; determined by animal’s response to painful stimuli</td>
<td>ED&lt;sub&gt;50&lt;/sub&gt; of propofol in infant mice determined to be 200 mg/kg</td>
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<td>Experiment 2: Propofol 25-300 mg/kg IP injection Control group saline injection</td>
<td>Immunohistochemistry assessed 6 h postexposure/activated caspase-3 staining</td>
<td>Propofol doses of 50 mg/kg and greater associated with significant neuronal apoptosis compared to control group</td>
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<td>Minimum propofol dose, which induced neuronal apoptosis was approximately one fourth the determined ED&lt;sub&gt;50&lt;/sub&gt; in infant mice</td>
</tr>
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<td>Fredriksson et al, 2004&lt;sup&gt;9&lt;/sup&gt;</td>
<td>P10 mice n = 16-24</td>
<td>Ketamine 50 mg/kg SC Diazepam 5 mg/kg SC Ketamine 50 mg/kg SC + Diazepam 5 mg/kg SC Vehicle (0.9% NS)</td>
<td>Fluoro-Jade B staining 24 h after exposure Behavioral tests for spontaneous motor activity and spatial learning performance</td>
<td>Apoptosis most pronounced in ketamine + diazepam group</td>
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<tr>
<td></td>
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<td>Decreased habituation and impaired spatial learning in ketamine alone and ketamine + diazepam groups</td>
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<tr>
<td>Jevtović-Todorović et al, 2003&lt;sup&gt;8&lt;/sup&gt;</td>
<td>P7 rats Long-term potentiation: n = 48 Behavioral studies: n = unknown</td>
<td>N&lt;sub&gt;2&lt;/sub&gt;O, isoflurane, or midazolam alone and in combination in varying doses and durations Midazolam 9 mg/kg IP + isoflurane 0.75 volume % + nitrous oxide 75 volume % × 6 h (triple cocktail) Control group received room air for 6 h or DMSO solution IP for midazolam control</td>
<td>Histopathology studies: Silver staining, activated caspase-3 staining, electron microscopy LTP: evoked responses of hippocampal slices Behavioral studies performed on rats exposed to “triple cocktail” and control group at multiple ages</td>
<td>Histopathology: N&lt;sub&gt;2&lt;/sub&gt;O alone and midazolam alone did not produce a significant increase in apoptotic neurons when compared to control animals. Animals treated with isoflurane alone showed dose-dependent neurodegeneration. Midazolam + isoflurane produced significant apoptosis compared with the same concentration of isoflurane alone. Triple-cocktail exposure resulted in “robust” apoptosis in all subjects, with more widespread damage than with midazolam + isoflurane. LTP: Triple cocktail produced significant suppression of LTP compared to other groups. Behavioral studies: Triple-anesthetic cocktail produced long-term spatial learning and memory impairments.</td>
</tr>
<tr>
<td>Stratmann et al, 2009&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Male P60 rats n = 40 Male P7 rats n = 141</td>
<td>Isoflurane 1 MAC 4 h exposure duration</td>
<td>Fear conditioning and spatial reference testing</td>
<td>Exposed rats had decreased performance in both spatial reference memory and fear conditioning training. Fear conditioning similar between exposed and control groups at 4 mo postexposure. At 5 mo postexposure, exposed rats demonstrated significantly decreased demonstration of conditioned fear.</td>
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</tbody>
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inhaled anesthetics. Both NMDA antagonists and GABA
mimetic agents have been extensively studied in animal
models. The majority of research utilized a rodent
model, involving mouse or rat pups. These studies have
unequivocally shown neuronal degeneration following
administration of anesthetic agents.8-10 Early research
by Olney et al 11 illustrated the potential for detrimental
effects of GABA-mimetic and NMDA antagonist activity
of ethanol in infant rats. Because of concerns regarding
generalizability to a human population, researchers have
recently begun utilizing infant primates as a more appro-
priate model.7,12

Concerns regarding the safety of anesthetic agents in
infants and children prompted the US Food and Drug
Administration (FDA) to launch a research program
entitled SmartTots (Strategies for Mitigating Anesthesia
Related Neurotoxicity in Tots), along with various non-
governmental agencies (see http://iars.org/smarttots).
The project aims to investigate the long-term effects of
anesthesia in infants and children. Facilities worldwide
have been recruited to gather data regarding the neuro-
developmental outcomes in pediatric anesthesia patients,
with results available in 2 to 5 years. This group of
studies will provide a more comprehensive picture of the
applicability of the animal research to a human popula-
tion.

Methods

A systematic review strategy was utilized to identify
articles pertinent to the literature review. Multiple lit-
erature searches were performed via the following search
engines: Academic Premier, CINAHL, and MEDLINE
through the Western Carolina University library. Search
keywords included neonatal, anesthesia, neuroapoptosis,
development, brain, neuronal, apoptosis, and degeneration.

The review was primarily limited to original research
published between the years 2000 and 2010, although
some fundamental knowledge articles were included
from years prior to 2000. Reference lists from pertinent
articles were reviewed for citations of additional articles
deemed relevant. Current clinical trials and research studies
were examined via the FDA website. The SmartTots program
was reviewed, and selected research abstracts presented by
the initiative are included in this review. A total of 71 articles
were selected from the literature for inclusion in this review. However, with careful
analysis 15 of the most pertinent studies were selected for
this manuscript. Twenty studies involved rodent models,
and 2 involved nonhuman primates. Six of which are presented here (Table 1), and 2 involved
subjects 6 of which are presented here (Table 2). Seven articles involved human
subjects 3 of which are included here (Table 3).

Table 1. Summary of Selected Experimental Studies Utilizing Rodents in Assessment of Anesthesia-Induced Neuronal Apoptosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Rodent Model</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viberg et al, 200816</td>
<td>P10 male mice</td>
<td>Ketamine 5 mg/kg SC</td>
<td>Protein analysis: for alterations in protein levels associated with neuronal survival, growth, and synaptogenesis</td>
</tr>
<tr>
<td>Zhang et al (2008)17</td>
<td>P7 mouse pups</td>
<td>Sevoflurane group: 1.7% sevoflurane + 30% O2 for 2 h</td>
<td>Immunohistochemistry: Cleaved caspase-3 detection single-strand DNA labeling to detect single-strand DNA seen during apoptosis</td>
</tr>
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</table>

Note: DMSO is a frequently used solvent in experimental protocols.
Background
All mammals undergo a specific period of synaptogenesis, or brain growth spurt, early in life, during which millions of neurons are formed and synaptic connections are made. During this time, brain growth is accelerated because of expansion of the dendrites from newly differentiated neurons, which form new synaptic connections. New neurons are formed, and many astroglia and oligodendroglia are created. The timeframe for the brain growth spurt period varies among species. In rodents, synaptogenesis begins just before birth, peaks at around 4 days postbirth, and continues for approximately 2 to 3 weeks. The human brain growth spurt commences in the third trimester of pregnancy, peaks at approximately 5 months of age, and lasts until 2 to 3 years of age.

Apoptosis, also known as programmed cell death or cellular suicide, is a natural and essential process in development and survival. The number of brain cells produced during synaptogenesis exceeds that which is required, and through the process of apoptosis extraneous neurons are eliminated. In addition, damaged or defective cells are removed via apoptosis throughout the lifespan. A variety of factors may initiate apoptosis, including various cytokines, hormones, drugs, and hypoxia.

Apoptosis is initiated by activated caspase-3, which attacks both the DNA of the cell as well as the cell’s cytoskeleton, producing DNA fragmentation and modulated plasma membrane components. Characteristic features of the apoptotic cell are condensation of the cytoplasm, blebbing of the plasma membrane, and apoptotic bodies containing intact cell organelles and fragments of the cell nucleus. These hallmark morphological changes associated with apoptosis are due to the effects of the caspase-3 protein.

Results
• Studies Using Rodent Models. The overwhelming majority of data suggesting that anesthetic exposure is neurotoxic to the developing brain are derived from research on rats and mice (see Table 1). While all studies examined for this review involved determination of apoptosis at a cellular level, researchers involved with some studies also evaluated neurobehavioral effects of anesthetic exposure in the weeks and months following exposure. The rodent’s spatial learning and memory, as well as motor activity, were a part of these assessments. Neurobehavioral effects were frequently assessed by the animal’s performance in various maze tests with novel environments and by evaluating the animal’s social interactions.

Some of the most compelling findings came from a 2003 study by Jevtovic-Todorovic et al. These researchers exposed 7-day-old rats to a combination of midazolam, isoflurane, and nitrous oxide for a total of 6 hours. The researchers found significantly increased apoptosis when rats were treated with midazolam plus isoflurane...
<table>
<thead>
<tr>
<th>Authors (y)</th>
<th>Sample type characteristics</th>
<th>Study purpose</th>
<th>Results and conclusions</th>
</tr>
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</table>
| DiMaggio et al, 2009<sup>19</sup> | n = 383 children who underwent inguinal hernia repair prior to age 3  
                     n = 5,050 children with no history of hernia repair in the first 3 years of life | Assess the association between hernia repair surgery before age 3 with the development of developmental and/or behavioral disorders. | Incidence of behavioral and developmental disorders for exposed group: 19.6 cases per 1,000 person-years.  
Incidence rate for the nonexposed group: 5.4 cases per 1,000 person-years.  
Cox proportional hazard model to control for age, sex, race, and confounding diagnoses at birth  
Authors assert a statistically significant association between hernia repair before age 3 and risk of behavioral or developmental disorders. |
| Dimaggio et al, 2010<sup>20</sup> | n = 11,648 children  
                     n = 668 exposed to anesthesia one or more times under 3 years of age | Evaluate association between anesthesia exposure under age 3 years and risk of developmental and behavioral disorders in a large cohort of twins. | Children exposed to anesthesia under age 3 years were more than twice as likely to develop behavioral and developmental disorders. (34.1 cases per 100 children vs 15.7 cases per 100 children). |
| Thomas et al, 2010<sup>3</sup> | n = 231 children who received general anesthesia prior to age 1 year  
                     n = 131 of these children had documented achievement test scores | Analyze the achievement test scores of children who received general anesthesia during infancy. | 11% of exposed children scored below the 5th percentile.  
Normative state scores: 5% scoring below the 5th percentile.  
Concluded that very poor academic performance was more likely in children who underwent general anesthesia prior to 1 year of age than among the normative population.  
Increased duration of anesthetic exposure produced significantly poorer academic achievement. |
| Wilder et al, 2009<sup>2</sup> | n = 5,357 children, 593 of whom received one or more general anesthetics prior to age 4 years | Determine whether an association exists between exposure to anesthesia prior to 4 years of age and the development of any learning disability | No increase in risk for development of a learning disability in children with a single anesthetic exposure (20.4% incidence).  
In children with 2 or more exposures, risk of learning disability was significantly increased (35.1% incidence). |

**Table 3. Summary of Selected Descriptive Studies Examining Long-Term Anesthesia Effects in Humans**
vs control animals. The neurodegeneration was found to be even more considerable when nitrous oxide was added to the midazolam/isoflurane combination (“triple cocktail”). This study utilized multiple methods of quantitatively and qualitatively evaluating neuronal apoptosis. The triple cocktail produced long-term impairments in spatial learning and memory, as well as deficiencies in acquisition and retention of information.8

Fredriksson et al9 also examined the effects of a combination of anesthetic agents, namely ketamine and diazepam. Rodents were assigned to 1 of 3 experimental groups (ketamine only, diazepam only, or ketamine plus diazepam) or 1 control group (normal saline injection). Researchers involved with this study found that not only was there significant apoptosis immediately following treatment, but also behavioral alterations persisted at 35 days postexposure. These effects were most pronounced among those rodents exposed to ketamine alone or to ketamine plus diazepam.9

Viberg et al10 evaluated mice at 2 and 4 months of age that had received ketamine, 5, 10, or 25 mg/kg at postnatal day 10. Testing consisted of spontaneous behavior observation, reflecting the animal’s ability to habituate to a novel environment, and the integration of sensory input into motor output. Testing at 4 months of age revealed significant dose-dependent deficiencies in all test variables.10 These results led this group of researchers to conclude that the apoptosis seen with ketamine administration in the neonatal mouse produced subsequent alterations in spontaneous behavior, learning, and memory. These deficits appeared to persist into adulthood, and were clearly dose-dependent and related to impedence of proteins vital to neurological development.

Zhang et al17 demonstrated an increased density in apoptotic cells following 2 hours of exposure to 1.7% sevoflurane in postnatal day 7 mice pups. These findings were confirmed utilizing both cleaved caspase-3 staining and single-stranded DNA labeling techniques. The researchers noted that the experimental concentration of 1.7% corresponds roughly to 0.75 minimum alveolar concentration (MAC) of sevoflurane, suggesting that even subclinical concentrations may be neurotoxic to the immature brain.17

In a 2009 study by Stratmann et al,18 7-day-old rat pups were exposed to 1 MAC of isoflurane for durations of 1, 2 or 4 hours. These rodents subsequently underwent testing at 8 weeks of age to evaluate fear conditioning and learning ability. Long-term neurocognitive deficits were observed only in those rat pups that had been exposed to 4 hours of isoflurane in infancy, as opposed to those exposed for 1 or 2 hours. This group displayed deficits in spatial reference memory and working memory.18

While studies looking at the effects of propofol use on the neonatal brain are limited, there are several recently-published studies specifically focused on this drug. Cattano et al4 determined the minimal dose required for induction of anesthesia in the neonatal mouse to be 200 mg/kg. They then treated groups of neonatal mice with intraperitoneal injections of propofol at doses from 25 to 300 mg/kg. The researchers saw significant histological apoptotic changes following treatment with propofol doses of 50 mg/kg and greater.4 These findings suggest that subclinical doses of propofol are capable of inducing neuronal cell death; the minimal apoptosis-inducing dose of 50 mg/kg is just 25% of the dose required for induction of anesthesia.

Studies Using Nonhuman Primate Models

There are limited studies using nonhuman primates to study the neurological effects of anesthesia exposure in infancy (see Table 2). Zou et al7 found that the neurotoxic effects of ketamine occur in both a dose and duration-dependent manner. These researchers found that exposure of 5- and 6-day-old rhesus monkeys to ketamine for durations of 9 and 24 hours produced significant increases in frontal cortex neuronal apoptosis compared to controls. However, an exposure time of 3 hours was not associated with significant histopathological differences between experimental and control groups. The selection of a 9-hour exposure was meant to reflect an exposure of extremely long duration, and the 24-hour exposure served as a positive control for ketamine-induced damage. The 3-hour duration was based on what the authors felt was a typical anesthetic exposure for the pediatric patient. The researchers suggest that ketamine-associated neurodegeneration is duration-dependent with exposure times of 3 hours or less appearing benign in neonatal monkeys.7

Brambrink et al12 exposed 6-day-old rhesus macaques to isoflurane at concentrations maintained between 0.7 and 1.5% end tidal for 5 hours. Immunohistochemical evaluation of the primate brains revealed a statistically significant increase in apoptotic cell density in those exposed to isoflurane, amounting to a 13-fold increase compared to controls. In the control group animals, apoptotic cells were sparse and randomly distributed. Conversely, the experimental group animals exhibited more abundant apoptosis that was concentrated in specific layers and regions of the brain tissue.12

Studies Using Human Samples

It is unclear to what extent research data on rodents and nonhuman primates can be extended toward understanding the effects of anesthesia in humans. The nature of this research innately limits the ability to feasibly and ethically conduct experimental research with human samples. For this reason, the current research continues to rely on rodent populations as well as the more recent use of nonhuman primate species. Whether or not findings in rodents or monkeys can reasonably be used to draw
conclusions in humans is debatable. For the medical community to determine whether anesthetic-induced neurodegeneration is a legitimate risk to infants and children entering the clinical setting, there must be evidence supporting the phenomenon in humans.

One strategy for studying the neurological effects of neonatal anesthesia in humans involves the use of retrospective cohorts. These studies seek to evaluate the presence of a significant relationship between early encounters with anesthesia and the subsequent development of neurocognitive or behavioral difficulties (see Table 3).

Dimaggio et al\(^1\) looked for a relationship between early anesthetic exposure and the presence of behavioral and learning disorders using a retrospective cohort of 383 children. The researchers obtained their sample from children who had undergone inguinal hernia repair prior to age 3. After controlling for age, race, sex, and the presence of any complicating birth-related diagnosis, the researchers found that inguinal hernia repair before the age of 3 approximately doubled the risk of subsequent diagnosis with a behavioral or learning disorder, a statistically significant finding.\(^1\)

Wilder et al\(^2\) performed a similar study involving the retrospective analysis of a birth cohort of 5,357 children. Medical records were reviewed to identify children who had undergone procedures necessitating general anesthesia before the age of 4. School records were reviewed to identify children diagnosed with learning disabilities in reading, writing, or math. Statistical analysis revealed that exposure to 2 or more general anesthetics before the age of 4 was associated with a 35.1% incidence of learning disability diagnosis. Children with no history of anesthetic exposure had only a 20% incidence of such a diagnosis.\(^2\) These were statistically significant findings; however, the authors acknowledge the limitation of multiple potential unidentified confounders.

An additional study performed by DiMaggio et al\(^3\) was a large twin study that enrolled 5,824 twin pairs. From this sample, 668 children had undergone anesthesia one or more times before age 3. In children with a history of anesthesia exposure, the incidence of developmental and/or behavioral disorders was more than double that of children with no history of exposure.\(^3\)

Academic performance is arguably one of the best indicators of neurocognitive development in children. Thomas et al\(^4\) evaluated the achievement test scores of 131 children ages 7 to 17 who had received general anesthesia during infancy (ie, exposed children). These scores were compared to statewide normative data. While the state normative scores below the fifth percentile accounted for just 5% of the population, 11% of exposed children fell below the fifth percentile. This information led these researchers to conclude that poor academic performance was more likely in children who underwent a general anesthetic prior to age 1. In addition, those children with increased duration of anesthetic exposure exhibited significantly poorer academic achievement, potentially reflecting the dose-dependent nature of anesthetic-induced neuronal injury.\(^3\)

The research of Kalkman et al\(^21\) examined the association between age at the time of first anesthetic exposure and the subsequent development of behavioral disturbances.\(^21\) They found behavioral disturbances were more common among the children in their sample who underwent anesthesia prior to age 2 years. Their data, however, failed to reach statistical significance, and the researchers cite the need for a larger sample size and further studies on the topic.

**Conclusion**

There is overwhelming evidence that exposure to various anesthetic agents causes neuronal apoptosis in neonatal animals; however, the applicability of this research to human populations is unknown. New data are rapidly becoming evident as researchers worldwide tackle this important topic. To see how this research applies to anesthetic practice, the anesthesia provider must understand basic concepts central to neuronal apoptosis and anesthetic toxicity.

The implications of the research on anesthesia induced neuronal apoptosis can be viewed as twofold: research implications and practice implications. The research implications are clear and are emphasized by the majority of authors proficient in the subject. Conclusive studies must meet many stringent requirements, and one challenge to the assessment of anesthesia-induced neuronal apoptosis is the selection of outcome measures. It is difficult to determine which measures best assess the effects of anesthesia upon neurocognitive or behavioral development. Four primary categories of clinical outcomes are generally thought to be central to the assessment of consequences of neuronal apoptosis in humans: cognitive functions (eg, IQ, academic performance), biomarkers (eg, serum and/or imaging studies), morbidity (eg, diagnoses of mental retardation, learning disability, etc), and mortality.\(^22\)

Conversely, the practice implications are vague and frequently speculative at this point. Multiple studies report combinations of anesthetic agents appear to produce more robust and widespread neuronal apoptosis than do single drugs.\(^8\)\(^-\)\(^9\) These findings lead some researchers to suggest a “less is more” technique, limiting the anesthetic to just 1 or 2 agents.\(^9\) Because of the dose-dependent nature of neuronal apoptosis in neonatal rodent models, other researchers propose limiting the duration of anesthetic exposure in neonates.\(^23\)\(^-\)\(^24\)

According to the FDA’s SmartTots Initiative, there is “no scientific basis for delaying essential surgery” (SAFEKIDS FAQ). However, the substantial evidence in animals clarifies the need for further investigation based...
on human models. Large-scale studies in humans, both retrospective and prospective, are needed to definitively confirm or refute the link between anesthesia exposure in neonates and long-term problems.

Several authors have described a number of methods of reducing the risk of neuronal injury from anesthetic exposure in young children. These include dexmedetomidine, lithium, melatonin, and others. Further research is needed in this area to determine the neuroprotective efficacy of such interventions.

It is the duty of the responsible anesthesia provider to be well apprised of the current data to protect the vulnerable pediatric population. Research employing human models is underway worldwide to better understand the long-term implications of neonatal exposure to anesthesia. Although such studies face a multitude of challenges, they are crucial in establishing a proper margin of safety for neonatal patients.

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