Cognitive Dysfunction in Children with Heart Disease: The Role of Anesthesia and Sedation

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ABSTRACT

As physicians and caregivers of children with congenital heart disease, we are aware of the increasing need for procedures requiring anesthesia. While these procedures may be ideal for medical and cardiac surgical management, the risks and benefits must be assessed carefully. There are well known risks of cardiovascular and respiratory complications from anesthesia and sedation and a potentially under-appreciated risk of neurocognitive dysfunction. Both animal and human studies support the detrimental effects of repeated anesthetic exposure on the developing brain. Although the studies in humans are less convincing of this risk, the Society of Pediatric Anesthesia jointly with SmartTots provided a consensus statement on the use of anesthetic and sedative drugs in infants and toddlers when speaking to families. (www.pedsanesthesia.org; http://smarttots.org/wp-content/uploads/2015/10/ConsensusStatementV910.5.2015.pdf). An excerpt of the statement is “Concerns regarding the unknown risk of anesthetic exposure to your child’s brain development must be weighed against the potential harm associated with cancelling or delaying a needed procedure. Each child’s care must be evaluated individually based on age, type, and urgency of the procedure and other health factors. This review provides a summary of the current evidence regarding anesthesia-induced neurotoxicity and the developing brain and its implications for children with congenital heart disease.

Key Words. Children; Congenital Heart Disease; Neurotoxicity; Anesthesia Exposure

Introduction

Findings from animal studies and preliminary translational human studies suggest that anesthetics may harm developing brains and this potential for anesthetic neurotoxicity, particularly in young children, is now a public concern.1–3 Multiple animal studies demonstrate that prolonged anesthetic exposure at a young age, when the brain is still developing, is associated with neurologic injury. Retrospective evaluations in humans also suggests that repeated anesthetic exposure at a young age might have detrimental effects on neurobehavioral outcomes.4,5 Children with congenital heart disease, even in the absence of anesthetic exposure, are already an “at-risk” population for poor neurologic outcomes.6–9 Though these children have predisposing risk factors, prolonged anesthetic exposure during surgical repair and repeated anesthetic exposure for multiple diagnostic procedures or a combination of the two may pose additional risks.

At the present time, how and to what extent exposure to anesthetics and other sedative medications affects cognition in children is not clear. However, given this potential for neurotoxicity and neurocognitive delay, caution must be exercised when ordering or recommending procedures requiring anesthesia or sedation in young children, with congenital heart disease.

Review of Existing Data

It is perhaps not surprising that consciousness-altering drugs that render people insensate could have neurotoxic side effects. The effects of maternal exposure to alcohol and other consciousness altering medications on the developing fetus are already well recognized.10 In fact, research on fetal alcohol syndrome, a known and permanent neurotoxic exposure, was the impetus behind examining

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Human/Translational Studies

Several studies in infants and children exposed to anesthesia and sedation while in infancy have been published. They all suffer from being retrospective with imprecise details of anesthesia and monitoring and small sample size (Table 2). A few notable ones are described below.

Kalkman et al. studied children (n = 314) who received anesthesia for urological procedures before the age of 6.25 Using the Parental Child Behavioral Checklist, they reported more behavioral disturbances in children who were anesthetized when they were under 2 years of age compared to older children. However, the authors concluded in a post hoc analysis that at least 2000 children would be needed to increase the sensitivity of the analysis to detect a difference between groups.

The Mayo Clinic Investigations, which followed4,5,26 used a birth cohort of 5357 children. In their initial study of children exposed to any anesthetic before the age of 4 years, only children exposed to more than one anesthetic had increased risk of learning disability compared to those who did not receive an anesthetic.5 In a subsequent analysis, examining only children less than two years of age exposed to anesthesia, again, one anesthetic exposure posed no discernible risk. With greater than two anesthetic exposures, these children had a 1.95 times greater risk for attention deficit hyperactivity disorder (ADHD)4 compared with children who were not anesthetized. However, concerns regarding their analysis include potential of confounding by comorbidities. The authors used ASA status to adjust for chronic and acute health conditions that also might place children at risk for behavior or cognitive problems. In addition, the level of paternal and maternal education and socioeconomic status were not evaluated. Parental education has consistently been an important association with neurodevelopmental outcome.27

Finally, the study4 was further limited by the small number of children exposed to anesthesia in infancy and the ethnically homogenous population of Olmsted County.

Using a birth data registry of twins from the Netherlands, the authors compared twin pairs in whom one child was exposed to anesthesia with an unexposed twin. Educational and cognitive scores during standardized assessment at age 12 did not differ by exposure to anesthesia before age 3 years.26 In a study from Denmark, 2689 children anesthetized for inguinal hernia repair in infancy were studied. The authors tested an age-matched control group and adjusted for known features associated with academic scores and reported no significant differences between those receiving anesthesia during infancy and those who did not have anesthesia.30 In a follow-up study using the same group, the authors identified children who underwent pyloric stenosis repair (<3 months of age) when compared to age-matched controls and adjusting for confounders found no statistical difference in tests scores.30

The Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) group from Columbia University31,32 used the New York State Medicaid Database to study the association between anesthetic exposure and neurodevelopmental outcomes. In the first study, age-matched controls exposed to anesthesia (for inguinal hernia repair) and unexposed children under the age of 3 were evaluated for behavioral outcome using ICD-9 codes. Children exposed to anesthesia had a HR 2.3 (1.3–4.1) for behavioral disorder compared to unexposed children. However this study was limited as the type of anesthetic agents used, the frequency and duration of anesthetic exposure were not defined as

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Table 1. Commonly Used Sedative Drugs and Anesthetic Neurotoxicity Studies in Animal Models

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Species</th>
<th>Dose</th>
<th>Exposure</th>
<th>Immediate outcome</th>
<th>Long-term outcome</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al. 1993</td>
<td>Nitrous oxide</td>
<td>Rats</td>
<td>25–57%</td>
<td>Continuous</td>
<td>Yes</td>
<td>No</td>
<td>No cell death</td>
</tr>
<tr>
<td>Jevtovic-Todorovic et al. 2003</td>
<td>Midazolam</td>
<td>Rats</td>
<td>50–150%</td>
<td>Single dose</td>
<td>Yes</td>
<td>Yes</td>
<td>No cell death alone; cell death when combined with isoflurane</td>
</tr>
<tr>
<td>Scaliet et al. 2004</td>
<td>Ketamine</td>
<td>Rat</td>
<td>10–20 mg/kg</td>
<td>Repeated every 30 min for 7 doses</td>
<td>Yes</td>
<td>No</td>
<td>20 mg/kg more cell death; no cell death with 10 mg/kg</td>
</tr>
<tr>
<td>Young et al. 2005</td>
<td>Ketamine</td>
<td>Mice</td>
<td>10–40 mg/kg</td>
<td>Single dose; alone or combined with versed</td>
<td>Yes</td>
<td>No</td>
<td>More cell death with higher doses alone and combination of agents</td>
</tr>
<tr>
<td>Young et al. 2005</td>
<td>Midazolam</td>
<td>Rats</td>
<td>9 mg/kg</td>
<td>Single dose; alone or combined with versed</td>
<td>Yes</td>
<td>No</td>
<td>No cell death alone only when combined with volatile</td>
</tr>
<tr>
<td>Fredriksson et al. 2005</td>
<td>Ketamine</td>
<td>Mice</td>
<td>25 mg/kg</td>
<td>Single dose; alone or combined with thiopental or propofol</td>
<td>Yes</td>
<td>Yes</td>
<td>More cell death with higher doses alone combination of agents</td>
</tr>
<tr>
<td>Ma et al. 2007</td>
<td>Nitrous oxide</td>
<td>Rats</td>
<td>75%</td>
<td>Alone</td>
<td>Yes</td>
<td>No</td>
<td>Nitrous or xenon alone did not cause cell death; xenon reduced isoflurane induced cell death</td>
</tr>
<tr>
<td>Cattano et al. 2008</td>
<td>Propofol</td>
<td>Mice</td>
<td>25–300 mg</td>
<td>Single dose</td>
<td>Yes</td>
<td>No</td>
<td>More cell death with higher dose; linear dose response curve</td>
</tr>
<tr>
<td>Xou et al. 2008</td>
<td>Nitrous oxide</td>
<td>Rats</td>
<td>75%</td>
<td>Continuous</td>
<td>Yes</td>
<td>No</td>
<td>Xenon alone induced apoptosis but reduced isoflurane induced apoptosis</td>
</tr>
<tr>
<td>Straiko et al. 2009able</td>
<td>Ketamine</td>
<td>Mice</td>
<td>40 mg/kg</td>
<td>Single dose</td>
<td>Yes</td>
<td>No</td>
<td>No cell death when administered alone</td>
</tr>
<tr>
<td>Pesic et al. 2009</td>
<td>Propofol</td>
<td>Rats</td>
<td>25 mg/kg</td>
<td>Single dose</td>
<td>Yes</td>
<td>No</td>
<td>Cell death reduced by lithium 3-6 mEq/kg</td>
</tr>
<tr>
<td>Sanders et al. 2009</td>
<td>Propofol</td>
<td>Rats</td>
<td>50–100 mg/kg</td>
<td>Single dose</td>
<td>Yes</td>
<td>Yes</td>
<td>Did not increase cell death; attenuated cell death induced by isoflurane</td>
</tr>
<tr>
<td>Becker et al. 2009</td>
<td>Propofol</td>
<td>Rats</td>
<td>30 mg/kg</td>
<td>Repeated</td>
<td>Yes</td>
<td>Yes</td>
<td>Cell death worse when compared to sevoflurane</td>
</tr>
<tr>
<td>De Roo et al. 2009</td>
<td>Propofol</td>
<td>Rats</td>
<td>20 mg/kg</td>
<td>Repeated hourly</td>
<td>Yes</td>
<td>No</td>
<td>Older aged animals; PND 15–30</td>
</tr>
<tr>
<td>Milanovic et al. 2010</td>
<td>Nitrous oxide</td>
<td>Rats</td>
<td>70%</td>
<td>2 hr pretreatment</td>
<td>Yes</td>
<td>Yes</td>
<td>No cell death in 2 hr and 4 hr exposure groups</td>
</tr>
<tr>
<td>Shu et al. 2010</td>
<td>Nitrous oxide</td>
<td>Rats</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td>Hypoxia worsened isoflurane induced cell death; nitrous no effect; xenon reduced isoflurane induced cell death</td>
</tr>
</tbody>
</table>
well as the likely possibility of under-ascertainment of ICD-9 miscoding to assess behavioral outcomes.31 In a follow-up sibling study of 138 exposed/nonexposed sibling pairs, they found a HR 1.6 (1.4–1.8) for behavior disorder, based on ICD codes. However, the population studied included mostly infants from low socioeconomic status and several infants were low birth weight, both these are well known risk factors for poor neurodevelopmental outcomes.32 The Western Australian pregnancy cohort (Raine) studied the association between anesthetic exposure prior to age 3 and neuro-developmental outcomes at 10 years of age.33 Of the 781 children, 112 had anesthesia exposure. When compared to unexposed children those exposed to anesthesia had some language and motor deficits but their academic achievement scores were similar. This highlighted the importance of outcome measures when interpreting studies of cognitive outcomes.44–46

Weaknesses are inherent in large, retrospective studies looking for a rare or hard-to-detect effect using administrative data, single-center data, and data from birth cohorts.37–40 Large datasets have been criticized for lacking detailed information about the anesthetic and surgery and being unable to control for the effects of migration patterns, comorbidity, and educational experience.40,41 Data from a single center may have more detailed information about the anesthetic, but are weakened by small study size. Birth cohorts of publicly insured children may not be generalizable to pediatric populations at large.40,41 These shortcomings in human literature continue to fuel the controversy as to whether anesthesia in infancy causes cognitive problems later in life.

Prospective single center studies are underway and could add significantly to the discussion and debate around the issue of anesthesia and sedation related neurotoxicity. The PANDA study31 (www.kidspandastudy.org) is examining children exposed to general anesthesia for hernia repair matched to unexposed siblings. Hernia repair requires a brief exposure to anesthesia (less than 1 hour) and is often required in infants. PANDA uses a prospectively administered comprehensive battery of neurocognitive tests. Results should be available in the near future. The MASK (Mayo Safety in Kids)42 study includes multiple exposures and examines children at two different ages in an effort to determine whether any observed effects persist into young adulthood. MASK employs an operant test battery, developed by the FDA to assess neurotoxicity in primates, as a part of the comprehensive neurobehavioral assessment and may allow direct comparison of primate findings with human data.42 Results should be available in 2017.12

The results of the first prospective multi-center, international randomized study comparing general and spinal anesthesia (GAS) in 722 infants has recently been reported. Less than an hour of sevoflurane anesthesia compared to awake-regional anesthesia for inguinal hernia repair did not increase the risk of adverse neurological outcome when evaluated at 2 years of age.45 The preliminary results at 2 years are an insignificant difference in Bayley Scales of infants and toddler development between the groups of 0.169 (−2.30 to −2.64). These findings are consistent with the animal studies, which show a dose-response relation to anesthetic exposure and neurotoxicity.44 The study plans a repeat neurological assessment at 5 years of age.

Hence at this point, neither the several retrospective studies in children nor the few prospective studies in otherwise healthy infants can decisively state that repeated or prolonged anesthetic exposure is without harm. This has special implications for children with congenital heart disease.

**Implications for Care of Children with Cardiac Disease**

Children with CHD, often require multiple diagnostic tests such as catheterizations, imaging, or echocardiography, requiring sedation or general anesthesia.45 It is our impression that the number of diagnostic tests requiring anesthesia in these children is increasing. At our institution, an infant with complex cyanotic congenital cardiac disease, prior to their initial surgical repair, could potentially undergo an echocardiogram, catheterization procedure, a MRI, or a CT, or possibly all four diagnostic procedures, each requiring an anesthetic exposure or if combined leading to one or more prolonged anesthetics.

There are conflicting data that choice of anesthetic medications impacts neurocognitive outcomes and pediatric data for anesthetic safety during cardiopulmonary bypass is very limited. In piglet studies of low flow cardiopulmonary bypass46 and circulatory arrest,47 the use of desflurane as compared to narcotic and droperidol, conferred neuroprotection. However, in recent studies by Andropoulous et al. examining neurodevelopmental outcomes after the arterial switch operation and after arch reconstruction, there is a suggestion that total midazolam dose negatively
Table 2. Landmark Retrospective Clinical Studies Evaluating Anesthetic Neurotoxicity: Listed in the Order of Publication

<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>Age of patients</th>
<th>Surgery</th>
<th>Anesthetic</th>
<th>Cases: controls</th>
<th>Outcome</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Maggio et al. 2009&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Birth cohort 1999–2001 New York State Medicaid</td>
<td>&lt;3 years of age</td>
<td>Inguinal hernia</td>
<td>Unknown</td>
<td>383:5050</td>
<td>ICD 9 codes for hernia repair and developmental delay, behavioral disorder, mental retardation, autism, language or speech problems. Controlled for GA, gender and weight. Male gender, birth complications and exposure to anesthesia increased risk.</td>
<td>Demographics limited to lower socio-economic class. Higher percentage of African American patients, 78% were male, higher proportion of low birth weight and prematurity in the population.</td>
</tr>
<tr>
<td>Bartels et al. 2009&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Young Netherlands Twin Registry 1986–1995</td>
<td>&gt;32 weeks GA (&gt;2000 g)-3 years</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Concordant exposed; concordant nonexposed; discordant; 1,143 monozygotic twin pairs (56% female)</td>
<td>Learning ability assessed at 12 years: Dutch Educational test (learning related outcome) and Conner's teacher rating scale for behavior. No difference in discordant pairs. Male twin pairs exposed had lower test scores than male twin pair not exposed. In discordant male pairs the exposed twin had lower scores.</td>
<td>Did not assess for learning disabilities nor address specific types of anesthesia.</td>
</tr>
<tr>
<td>Wilder et al. 2009&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Mayo Clinic I; 1986–1990</td>
<td>&lt;4 years of age</td>
<td>Unknown</td>
<td>Unknown</td>
<td>593:4764; 449 single exposure; 100 two exposures; 44 three exposures</td>
<td>Learning disability: 3 formulas for IQ and achievement test scores until age 19. Adjusted for GA, gender and weight. More than one anesthetic and duration &gt;120 min statistically significant.</td>
<td>Not adjusted for level of maternal education. Not sure if anesthesia exposure is an associative marker for other factors that contribute to risk. Lack of homogeneity and generalizability of the population studied. Is LD an appropriate outcome measure?</td>
</tr>
<tr>
<td>Flick et al. 2011&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Mayo Clinic 2; 1986–1990</td>
<td>&lt;2 years of age</td>
<td>Unknown</td>
<td>Unknown</td>
<td>350:700</td>
<td>Health status was quantified using ASA and JHACGCM. Assessed for LD and need for IEP in addition to IQ tests. No risk for emotional behavioral disorder regardless of number of exposures. Speech and language was impaired with &gt;2 exposures.</td>
<td>Halothane was used in this subset of patients and is no longer a clinically used anesthetic. Cannot distinguish between the effects of surgery, hospital stay and number of visits to the hospital.</td>
</tr>
<tr>
<td>DiMaggio et al. 2011&lt;sup&gt;32&lt;/sup&gt;</td>
<td>New York Medicaid birth cohort; twin siblings 1999–2005</td>
<td>&lt;3 years of age</td>
<td>Inguinal hernia repair</td>
<td>Unknown</td>
<td>138 discordant pairs</td>
<td>No difference in concordant pairs; no difference in discordant pairs. 60% of exposed children had an ICD diagnosis of learning or behavior problems</td>
<td>Similar to 2009 study</td>
</tr>
<tr>
<td>Sprung et al. 2012&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Mayo Clinic 3; 1986–1990</td>
<td>&lt;2 years of age</td>
<td>Unknown</td>
<td>Unknown</td>
<td>350:700</td>
<td>ADHD identified; &gt; 2 anesthetics increased risk</td>
<td>Same as prior 2 studies</td>
</tr>
<tr>
<td>Ing et al. 2012&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Western Australia Pregnancy Cohort I; 1989–1992</td>
<td>&lt;3 years of age</td>
<td>Various</td>
<td>Unknown</td>
<td>321:2287</td>
<td>Multiple neuropsychological testing over 16 years. Exposed subjects had a higher incidence of receptive and expressive language and abstract reasoning deficits.</td>
<td></td>
</tr>
<tr>
<td>Hansen et al. 2013&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Danish birth cohort 1986–1990</td>
<td>Less than 3 months</td>
<td>Pyloric stenosis</td>
<td>Unknown</td>
<td>779:14,665</td>
<td>Nationwide standardized test in 9th grade; adjusted for gender, birth weight, parental age and education, jaundice. Exposed to anesthesia group had lower test scores but no statistically significant difference</td>
<td>Anesthesia used in this cohort may not be that used currently. Higher incidence of unavailable test scores in the exposed group</td>
</tr>
<tr>
<td>Ing et al. 2014&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Western Australia Pregnancy Cohort II; 1989–1992</td>
<td>&lt;3 years of age</td>
<td>Various</td>
<td>Unknown</td>
<td>112:669</td>
<td>Extensive testing at 10 years of age. Exposed individuals had increased incidence of behavior, language and cognitive abnormalities by testing and ICD-9 codes but no difference in academic achievement tests</td>
<td></td>
</tr>
</tbody>
</table>

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affected neurodevelopmental outcome though the surgical exposure and underlying disease may account in part for the diminished neurodevelopmental function.\textsuperscript{48,49} In another study of 135 infants with CHD undergoing surgery, the total days patients received benzodiazepines or chloral hydrate, but not the total doses were associated with poorer neurodevelopmental outcomes in follow-up neurocognitive studies, though the effect size was modest.\textsuperscript{50}

Multiple animal studies, including nonhuman primate studies demonstrate the neurotoxic effects of propofol administration at clinically relevant concentrations.\textsuperscript{51–54} Rodent, nonhuman primate, and human translational studies consistently reported neurotoxicity associated with ketamine use.\textsuperscript{16–18} In infants, the largest negative effects on neurocognitive outcome were associated with: single ventricle, use of hypothermic arrest during surgery, antenatal diagnosis, and administration of ketamine.\textsuperscript{55} However given these clinical factors, the association with ketamine use was no longer statistically significant. Despite the potential for negative neurodevelopmental outcomes, use of ketamine in complex and unstable patients is common, given its favorable hemodynamic effect profile.\textsuperscript{56,57}

Since developmental anesthetic neurotoxicity has largely been associated with the combination of GABAergic and NMDA antagonist actions of anesthetic drugs, dexmedetomidine, which is neither a GABAergic nor NMDA antagonist may be safer.\textsuperscript{58} Dexmedetomidine reduced neuronal apoptosis in a dose-dependent manner in neonatal rats. However, this is the only study we know of to date where an intervention protected both from anesthesia-induced cell death and anesthesia-induced neurocognitive dysfunction. These results require confirmation in additional animal and prospective human studies.

**Conclusion**

Anesthesia and sedation for the many diagnostic and interventional procedures required in children with congenital heart disease is a genuine safety concern. In addition to the often complex hemodynamic changes attributable to the administration of anesthetic drugs, there is now additional growing concern that anesthesia may induce neurotoxicity and result in neurocognitive dysfunction. However, the number of procedures requiring anesthesia and or sedation in these children is growing and the cumulative effect of these repeated exposures on the developing brain is unknown. Currently, it is unclear whether a change in clinical anesthetic practice is warranted, as there are no superior alternatives (www.SmartTots.org). Additional investigations are urgently needed to evaluate the impact of multiple anesthetic exposures in the developing brain and the specific neurocognitive deficits resulting from the exposure. Further, the additional exposure to sedatives and analgesic medications in the intensive care will likely add to the risk of adverse outcomes.

Based on current evidence, we recommend a thoughtful approach to requests for sedation and anesthesia in children given the potential neurotoxic effects of all commonly used agents. Physicians caring for these patients, cardiologists, anesthesiologists, surgeons, and intensivists, must be prepared to discuss the potential toxicity of exposure to medications not only during diagnostic studies but subsequent surgery and intensive care stay with families. Recommending procedures requiring anesthesia or sedation in infants and children must be balanced with the value of information obtained and potential risks. This is especially true for children already at increased risk for neurocognitive deficits, like those with congenital heart disease.

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