The Effect of General Anesthesia on the Developing Brain: Appreciating Parent Concerns While Allaying Their Fears

by Luke S. Jank, MD

More than one million children under the age of five undergo surgery annually in the United States.1,2 The most common procedures are myringotomy tubes, tonsillectomy/adenotonsillectomy, hernia repairs, and circumcisions. Recently, the issue of anesthesia-related neurotoxicity has been in the media limelight, and parents are appropriately fearful about the effects of general anesthesia on their child’s brain development.

Any anesthesia professional who cares for children has undoubtedly faced the question, "Will anesthesia harm my child's brain?" It is no wonder parents are frightened about the effects of general anesthesia on the developing brain. A quick Google search of this very question yields over 400,000 results, with attention grabbing headlines such as, "Anesthesia May Harm Children's Brains" (WebMD)3 and "Researchers Warn on Anesthesia, Unseen Risk to Children" (NY Times).4 Are these concerns justified or is this media sensationalism? As anesthesia professionals, what are our responsibilities to the parents in discerning the risks of general anesthesia? The following review on this topic will address the pre-clinical evidence, observational studies, and the most recent research efforts.

Pre-Clinical Evidence

In 2000, Ionomonodou et al. published a landmark article in Science investigating the mechanism of ethanol in the development of Fetal Alcohol Syndrome (FAS).5 By treating rat pups with ethanol during the peak period of brain synaptogenesis, they were able to replicate the effects of FAS including generalized loss of brain mass and neuronal apoptosis. They discovered that ethanol causes widespread apoptotic neurodegeneration by two distinct mechanisms: N-methyl-D-aspartate (NMDA) antagonism, and γ-aminobutyric acid receptor (GABA) activation.6 Not surprisingly, this study caught the attention of the anesthesia community, as many of our anesthetic and sedative act by one or both of these mechanisms.

Over the following years, hundreds of studies in various animal models including rodents and non-human primates convincingly demonstrated a link between anesthetic agents and neurotoxicity.7,8 Nearly all of our commonly used anesthetic agents have been identified as culprits, including benzodiazepines, propofol, ketamine, volatile anesthetics, and nitrous oxide.9,10 Do the findings of these animal studies translate to the effects on humans undergoing anesthe-sia? The dose and duration of anesthetic exposure in the animal models is considerably higher than what an infant is typically exposed to in the operating room. In addition, there is interspecies variability in drug potencies, toxicities, and side effect profiles. Furthermore, each animal model has a different window of neurotoxicity and different rates of brain maturation. These challenges significantly limit our ability to draw a meaningful conclusion, not to mention the fact that animal models often lack the precise physiologic monitoring, resuscitation efforts, and controlled ventilation that are utilized in real-time clinical practice.

Observational Studies

Given the inherent limitations of animal models, focus shifted from the laboratory towards human clinical trials. Numerous retrospective observational studies were published that suggested anesthetic exposure early in life was a risk factor for learning disabilities later in life. Ing et al. reviewed test scores of language, cognition, motor skills, and behavior in a cohort of three hundred 18-year-olds who were exposed to anesthesia before age 3. These children were found to have a higher risk of language and abstract-reasoning deficits than unexposed matched controls.11 Flick et al. compared a similar cohort of children exposed to anesthesia prior to age 2 to unexposed matched controls. They suggested that exposure to multiple— but not single—anesthetics was an independent risk factor for the later development of learning disabilities.12 Wilder and colleagues also found that exposure to multiple anesthetics before the age of 4 was a significant risk factor for the development of learning disabilities.13

While many observational studies support a link between exposure and disability, a similar number of studies refute this claim. In 2011, Hansen and colleagues reviewed ninth grade standardized test scores in over 2,500 children who underwent inguinal hernia repair in infancy, and found that compared to age-matched controls, there was no evidence of increased learning disabilities when adjusting for known confounders.14 The same author later showed that over 700 infants exposed to anesthesia for pyloric stenosis repair before 3 months of age had similar educational test scores in adolescence compared to the unexposed controls.15 Bartels and colleagues performed a monozygotic concordant-discordant twin study of over 1,000 twin pairs in which one sibling was exposed to anesthesia prior to age 3 and the other was unexposed. They found the exposed twin had similar scores on standardized tests at age 12 as the genetically identical unexposed twin, suggesting that anesthesia exposure was not a risk factor for poor test scores.16

The results of these small observational studies are conflicting, and do not provide a definitive answer to the question at hand. Rather, the conflicting data highlight the weaknesses of retrospective studies. Controlling for potential confounders including birth weight, gestational age, parental age and education, socioeconomic status, income, and ethnicity, proves to be very difficult. In addition, utilizing standardized achievement tests as outcome measures may not detect subtle neurocognitive deficits. Moreover, given the nature of retrospective studies, the individual anesthetic records are usually not available for review, so the anesthetic agent(s), dose, and duration of exposure are often unknown.17,18,19

Recent Advances

Three recent large, well-designed studies have furthered our understanding of how general anesthesia impacts neurodevelopment. The General Anesthesia compared to Spinal Anesthesia (GAS) trial is an international, multicenter, observer-blinded, randomized controlled trial in which infants (less than 60 weeks postmenstrual age, born greater than 25 weeks gestation) undergoing inguinal hernia repair were randomly assigned to receive either sevoflurane general anesthesia or awake-regional anesthesia by spinal, caudal, or combined spinal-caudal technique.20 The primary outcome is the score on a validated Intelligence Quotient (IQ) test administered at age 5, and is pending study completion in 2017. The secondary outcome was recently reported in Lancet, assessing neurodevelopment at age 2 by grading cognitive tasks such as attention, memory, and problem solving, in addition to motor and language skills. Davison et al. found no evidence that less than one hour of sevoflurane anesthesia in infancy increases the risk of adverse neurodevelopmental outcome at age 2 compared to the awake-regional group.21

Sun et al. recently published another landmark trial, the Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) study.22 This study compared neurocognitive and behavior outcomes in children aged 8–15 years old exposed to a single general anesthetic for inguinal hernia surgery prior to age 3 to their unexposed sibling. The results suggested no statistically significant difference in full-scale IQ score between the exposed and unexposed siblings.23 There were also no statistically significant differences between groups in

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scores of memory, executive function, motor and processing speed, language, attention, visuospatial function, or behavior. The results reported were strengthened by the study's use of sibling-matched controls (which reduced confounders, e.g., genetics, socioeconomic status, and parental educational level) and the ability to review the anesthetic record, which provided insight into the type and duration of anesthetic exposure.

Most recently, O'Leary et al. published a large population-based cohort study assessing developmental outcomes at primary school entry (age 5-6) in over 25,000 children exposed to general anesthesia compared to more than 55,000 matched controls. In the first "big data" study in this field, they found no evidence of adverse developmental outcomes in children exposed to anesthesia before age 2, or in those with multiple exposures to anesthesia. While there was a very small risk of adverse developmental outcomes in children exposed after age 2, the significance and cause of this finding remains unclear. Perhaps this is a result of the anesthetic, but seeing that there was no adverse developmental outcome in over 10,000 children exposed under age 2—considered the "window of vulnerability" in human neurodevelopment—we can speculate that another cause may be responsible (e.g., the underlying disease process or other unaccounted for confounding variables). As alluded to in the previous section, one inherent limitation of observational studies is that they cannot prove causality.

Discussion

Many pediatric anesthesiology professionals are reassured by the results of the recent studies discussed above, but recognize that the data are not conclusive, and further research is necessary before we can definitively state that a single exposure to a short anesthetic has no adverse effect on neurodevelopment. Until then, how can anesthesiology professionals ease the concern among parents whose children undergo procedures requiring anesthesia? First, we can stress to parents that it is widely accepted that infants and children require anesthesia for a variety of common procedures and that delaying these procedures has clear inherent risks as well. Next, we can highlight that to-date, the most recent well-designed, large-scale studies reassuringly show minimal or no impairment in neurocognitive development in children who received general anesthesia (though we still await the primary endpoint in the GAS study). Lastly, we can discuss that there is no evidence suggesting that one anesthetic technique is preferred over another. Therefore, the choice of anesthetic technique should be left up to the discretion of the anesthesia team on a case-by-case basis.

Anesthesia professionals can point parents to the SmartTots website (www.smarttots.org), which is a collaboration between the International Anesthesia Research Society and the FDA to coordinate and fund research on the topic of anesthesia and neurodevelopment. This website contains useful resources and a consensus statement created by experts in the field on this topic for both parents and professionals. As an anesthesia professional, we should listen to parents and acknowledge their fears, while providing them with evidenced-based recommendations and credible resources. This may help to ease their worry, while mitigating their fears related to the effects of anesthesia on their child's developing brain.

References


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