REVIEW ARTICLE

Anesthetic Neurotoxicity in Infants and Children: A Review of the Literature

Abstract

The clinical pediatric anesthesiology community has been greatly affected by a growing body of research suggesting that sedative drugs and anesthetic agents may have long lasting detrimental neurocognitive effects in children. Various animal models have indicated apoptotic brain cell death and neurocognitive impairment following anesthetic exposure in early life. Although these studies cannot be directly extrapolated to anesthesia in children, parents and governmental regulatory agencies have been paying attention nonetheless. Adding to the evidence are a number of human epidemiologic studies that have documented neurologic deficits and cognitive decline following early anesthetic exposure.[1-4] Clinical studies in children exposed to general anesthesia have assessed outcome measures including academic performance or school readiness, validated neuropsychologic testing, and educational interventions for neurodevelopmental or behavioral problems.

Aim

The purpose of this manuscript is to review the most recent clinical studies providing evidence that the concerns regarding anesthetic neurotoxicity may be overstated in healthy children who require anesthesia.

Introduction

Healthcare providers face a profound dilemma, in that denying adequate analgesia to children may incite hyperalgesia, altered pain processing, chronic pain syndromes and behavioral problems,[5] while providing anesthesia for necessary interventions may also be detrimental. Further compounding this conundrum, practitioners do not have proven safe alternatives to our current anesthetic regimen, and young children often require diagnostic tests or surgical interventions that cannot be deferred. There are a variety of confounding factors that add to the complexity of this topic. Patient co-morbidities, as well as environmental, biological and social factors may make specific pediatric populations more vulnerable to anesthetic neurotoxicity. This review article provides an overview of animal data and human clinical trials pertaining to the effects of anesthetics on the developing brain.

Anesthesia in Newborns

Preterm and full-term infants routinely undergo general anesthesia for surgical interventions and imaging studies. The advent of volatile anesthetics with reduced myocardial depressant effects and enhanced monitoring techniques has enabled critically ill infants to undergo anesthesia with increased safety. Immature animal models have shown enhanced neuroapoptosis following exposure to almost all anesthetic agents. Hypocapnia and perioperative hypotension may also have marked adverse effects on infant neurocognitive development. The importance of anesthesia in reducing perioperative morbidity and mortality as well as the surgical stress response has been demonstrated by Anand and Hickey.[6] A randomized trial of newborn patients by Anand et al[7] undergoing ligation of a patent ductus arteriosus demonstrated that fentanyl in combination with nitrous oxide and a paralytic improved postoperative outcomes by blunting metabolic and circulatory complications. Similarly, Rao et al[8] demonstrated patients undergoing gastroschisis repair without anesthesia had a higher incidence of bowel ischemia, need for total parenteral nutrition and unplanned reoperation as compared to neonates who received anesthesia.

Although the safety of pediatric anesthesia has improved significantly over the last 6 decades, with a current perioperative mortality rate of 0.9/10,000 anesthetics, neonatal mortality is disproportionately higher than other age groups.[9,10] Neonates exhibit a 6-fold increased mortality rate compared to infants less than 1 year of age, and 25 fold higher mortality versus children less than 18 years old. Flick et al[11] found that neonates have 69 times greater mortality during anesthesia than children older than 10, largely attributed to infant physiology, perioperative co-morbidities and the high incidence of congenital heart disease. Poor perioperative outcomes in neonates are largely dependent on the timing of anesthetic exposure, with the youngest infants at highest risk. Hypoxia, hypotension and hypoglycemia are also associated with

adverse neurocognitive outcomes in this population.

Hypotension and Hypocapnia in Infants

Neonatal literature defines hypotension as a reduction in mean arterial blood pressure (MAP) below the 5th -10th percentile for gestational age. Most experts claim that maintenance of the MAP within the limits of cerebral autoregulation is ideal for neuroprotection. In infants with open fontanelles, the lower limits of cerebral autoregulation are not well defined. There have been different parameters set on this value, in 1992, the Joint Working Group of the British Association of Perinatal Medicine[12] recommended the MAP not fall below the infants gestational age in weeks. Vavilala et al[13] found that in infants less than 6 months of age, the lower limit of autoregulation is 38 mmHg, or a 20% reduction of MAP from the awake state. In infants older than 6 months of age, the lower limit of autoregulation occurred when MAP decreased by 40%. Inadequate cerebral perfusion from hypotension can lead to ischemia and damage to cerebral watershed zones.

A 2014 case series by McCann et al[14] examining 6 infants less than 48 weeks postmenstrual age claimed that perioperative hypotension was directly linked to postoperative encephalopathy, likely secondary to cerebral hypoperfusion. In this study, intraoperative anesthetic records revealed systolic blood pressure < 60mmHg, along with prolonged periods of mild hypocapnia ($PaCO_2$ < 35 mmHg). Infants presented with new onset seizures within 25 hours of anesthetic administration, caused by supratentorial watershed infarcts between the anterior, middle and posterior cerebral arteries. This unfortunate case series had one infant death, one infant with profound developmental delays, one with minor motor delays, two normal infants and one lost to follow-up. While general anesthesia is associated with reduced cerebral metabolic rate and oxygen consumption in adults, this is not the case in infants. Both intravenous and volatile anesthetic agents are excitatory to the infant brain.

Cerebral blood flow (CBF) is highly regulated by the partial pressure of arterial carbon dioxide ($PaCO_2$). Hypocapnia leads to cerebral vasoconstriction and reduced CBF, with potential for cerebral ischemia in the neonatal population.[15] A study by Fabres et al[16] scrutinized clinical data and blood gas values during the first four days of life in very low birth weight infants, finding that neonates with a $PaCO_2$ < 39 had a 27% incidence of severe intraventricular hemorrhage (IVH). They claimed optimal CO_2 values were between 39 and 60 mmHg, and infants within this range exhibited a much lower 3% incidence of severe IVH. Similarly, a randomized trial by Resch et al[17] found that during cooling in encephalopathic infants > 36-weeks gestational age, $PaCO_2$ < 35 mmHg was associated with periventricular leukomalacia. Capnography may not be a reliable measurement of $PaCO_2$ in infants with lung disease or very low birth weight, and capillary or arterial blood gas measurements may be required to prevent sustained hypocapnia.

Animal Studies of Anesthesia-associated Neurotoxicity

Studies in animal models suggest long-lasting deficits in memory and learning following anesthetic exposure in infant animals. There are two classes of anesthetic agents primarily implicated in neuronal apoptosis: N-methyl-D-aspartate (NMDA) antagonists (i.e. nitrous oxide and ketamine) and gamma-amino-butyric acid (GABA) agonists (i.e midazolam, propofol and volatile anesthetics). A groundbreaking study revealed widespread neuroapoptosis in rat pups following exposure to midazolam and nitrous oxide in 1999.[18] Subsequent studies demonstrated accelerated apoptosis in young rodents, nematodes, piglets and primates following exposure to most general anesthetic agents including benzodiazepines, nitrous oxide, isoflurane, sevoflurane, thiopental, propofol and ketamine.[19]

Although neuroapoptosis is a normal part of mammalian development, animal experiments revealed maladaptive patterns of apoptosis that lead to developmental impairments.[20] The greatest effects were seen in rats less than 7 days old or neonatal primates who experienced longer exposures to NMDA and GABA agents.[21] In addition to apoptosis, animals exhibited alterations in dendritic spines and astroglial development, detrimental effects on neurogenesis, reduced synaptic density, degeneration of mitochondrion and reduced neurotrophic factors.[22] Alarmingly, non-human primates have exhibited long-term altered behavior and learning potential.[23] The translation of these findings in animals is uncertain when applied to humans. In animal models, researchers are limited by the lack of continuous hemodynamic monitoring as well as repeated measurements of acid-base status and glucose levels, the standard of care for complex procedures in human neonates. In rodents, there is high risk for hypercarbia, metabolic acidosis and hypoglycemia leading to neurologic compromise during anesthesia. In clinical practice, these derangements would be expeditiously addressed.

Extrapolation of animal data to clinical relevance requires a defined susceptibility period as well as an identifiable dose and duration of anesthetic that leads to measurable neurotoxicity in humans. Of note, animal models have utilized relatively large doses of anesthetic agents her kilogram of body weight as well as significantly prolonged lengths of exposure. Taking into account that an average animals life's span is appreciably shorter than the average human, it is difficult to translate how length of anesthetic exposure applies to humans. Animal models have indicated a neuroprotective role for agents such as dexmedetomidine, xenon, melatonin and β-estradiol.[24]

Human Trials of Anesthesia related neurotoxicity

Human infants undergo their most rapid brain growth between 28-weeks gestational age to 2-years-old. Most epidemiological cohort studies have investigated children younger than 4 years of age. The data from these human trials is mixed, with some showing

poor neurodevelopmental outcomes in children exposed to general anesthesia, while others find no link even amongst sibling and twin studies. (See Table 1 for summary data). Eckenhoff et al[25] first linked general anesthesia to debilitating neurologic effects in 1953. This group claimed that night terrors, bed wetting, temper tantrums, and fear behaviors were observed in young children following exposure to vinyl ether, ethyl chloride, and cycloprone for otolaryngologic surgery.

A population most closely followed with neurocognitive testing are neonates and infants undergoing corrective or palliative congenital heart surgery, such as those with hyoplastic left heart syndrome. The literature documents significant neurocognitive impairment in these infants, likely due to abnormal preoperative brain function, reduced perioperative oxygen and cardiac output, the utilization of cardiopulmonary bypass, deep hypothermia, circulatory arrest, and regional cerebral perfusion abnormalities.[26] Bellinger et al[27] examined standardized testing in infants who underwent the neonatal arterial switch operation, documenting abnormalities in motor and cognitive development. These persistent cognitive defects may be due to repeated anesthetic exposures.

Critically ill infants with necrotizing entercolitis[28] necessitating surgical intervention with anesthesia experienced a growth delay and adverse neurodevelopmental outcomes compared to infants who were medically managed. These results may be confounded by the fact that extremely low-birth-weight infants were more critically ill and required higher inotropic support. DiMaggio et al[29] examined children less than 3 years of age who underwent hernia repair under general anesthesia and compared them to an age-matched cohort who were unexposed. After controlling for congenital disease and gender, the children who underwent hernia repair were more than twice as likely to be diagnosed with a developmental or behavioral disorder.

A 2009 study by Wilder at al[2] from the Mayo Clinic examined a cohort of 5000 children from birth through their school age years, finding an increase in learning disabilities in children exposed to 2 or more anesthetics. Bartels et al,[30] on the other hand, examined Dutch monozygotic twin pairs, and found that intellectual achievement was similar between the anesthesia- exposed and unexposed twins.

A population-based Canadian study by Graham et al[31] examined the association between surgical exposure in young children and scores on the Early Development Index (EDI), an exam gauging school readiness. This group found a weak association between early anesthesia exposure and low EDI score when adjusted for age, gestational age at birth, and socioeconomic factors. Increased risk was apparent in children exposed to anesthesia at greater than 2 years of age, although there was no association with exposure to multiple anesthetics.[31] This lead the authors to suggest that these conflicting findings may be due to unknown confounders.

The Pediatric Anesthesia and Neurodevelopmental Assessment (PANDA)[32] study is a large cohort study examining 105 sibling pairs from four different pediatric centers compared to a group of children 8-15 years of age who underwent hernia repair prior to age 3. Children who underwent surgery are compared to their siblings less than 36 months apart on a battery of neurodevelopmental tests examining full scale IQ as the primary outcome. This group found that there were no differences in performance and verbal aspects of IQ, motor skills, processing speed, language, visuospatial, attention and executive function or behavioral skills in children exposed and unexposed to anesthesia.

The 2016 General Anesthesia Compared to Spinal Anesthesia (GAS) trial[33] is the first randomized controlled trial to compare general to regional anesthesia for inguinal hernia repair in healthy infants. Following < 80 minutes of exposure to sevoflurane anesthesia versus spinal anesthesia, there was no difference in cognitive testing found at age 2. The 5-year outcome of IQ score is pending in 2021. In 2017, Ing et al[34] investigated anesthesia exposure prior to age 5 in 38,493 children undergoing common surgical procedures (pyloromyotomy, inguinal hernia repair, tonsillectomy, and circumcision outside the neonatal period). Exposed children were propensity score-matched to 5 controls, on 50 covariates including sociodemographic factors, medical comorbidities and health care utilization. The study concluded that the hazard ratio for childhood mental disorders was 1.26, with an increase observed specifically for developmental delay and ADHD.

It is important to note that findings of adverse effects on learning, memory and cognition following anesthesia should not be examined in a vacuum. Confounders related to perioperative risk factors, patient comorbidities, surgery length and type, underlying pathology, and environmental factors, should also be examined closely. In this vein, some epidemiological neurotoxicity studies have attempted to control for comorbid conditions, including congenital heart disease, and socioeconomic factors, such as maternal level of education, to examine the effect of anesthesia on children's developmental outcomes.

Conclusion

The clinical evidence for anesthesia-related neurotoxicity in humans is not entirely clear. With regards to neurotoxicity in humans, prospective, randomized placebo-controlled trials are not possible and confounders limit retrospective studies. In 2016, the US Food and Drug Administration (FDA) released a safety advisory advising that prolonged use of general anesthesia (> 3 hours) in infants less than 3 years old or pregnant women in their third trimester, may adversely affect children's brain development. This safety announcement applies to 11 anesthetic and sedative medications including benzodiazepines.[35] SmartTots, (Strategies for Mitigating Anesthesia-Related Neuro-Toxicity in Tots), the public private partnership between the FDA and the International Anesthesia Research Society, is

committed to funding research to ensure the safety of anesthesia for infants and children. As anesthesia is necessary for infants, children and pregnant women undergoing time-sensitive imaging, surgery, and other painful procedures, practitioners should aim to weigh the risks and benefits of anesthetic administration with each patient encounter.

Although further research is needed on anesthesia related neurotoxicity, the current data does not support a change in pediatric anesthesia practice. In response to the warning by the FDA, the American Academy of Pediatrics engaged in a coordinated response to reassure practitioners and parents that most studies show no developmental problems associated with a single short anesthetic exposure. There are incongruous study results based on the human trials discussed in this review. Although retrospective in nature, a number of independent studies have found no association between anesthesia and maladaptive cognitive outcomes in healthy children less than 2 years-old, even with multiple anesthetic exposures. Although more work is yet to be done, these studies suggest that there is minimal or nonexistent long term neurodevelopmental risk associated with single anesthesia exposure in healthy infants and children. Biological, social and environmental factors may be more important in the determination of children's cognitive potential. Future studies may look to focus on specific populations and procedure types that place the young brain at greatest risk during anesthesia.

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Summary of Anesthetic Exposure Associated Neurotoxicity in Human Trials

Year	Study	Design	Population	Findings	Procedures	Outcome Measures
2009	Wilder et al	Retrospective birth cohort study	5,357 children < 4 years-old	Increased risk of learning disabilities with exposure to 2 or more anesthetics	All	Learning Disabilities
2009	Bartels et al	Twin	1,143 Monozygotic Twin pairs < 3 years- old	Similar intellectual ability among twins	All	Group test of achievement, teacher rating
2009	Kalkman et al	Retrospective pilot study	314 children 0-6 years-old	Children < 24 months old showed more behavioral disturbances than those > 2, although not statistically significant; larger sample size needed for definitive results	Urological procedures	Parental Child Behavior Checklist
2010	Walker et al	Prospective observational cohort study	43 infants with pyloromyotomy, 211 control infants < 1 year-old	Infants with pyloric stenosis repair scored lower on the cognitive, receptive language, fine motor, and gross motor subscales compared to controls	Pyloric Stenosis	Bayley Scales of Infant and Toddler Development
2011	Hansen et al	National birth cohort study	2,689 children undergoing hernia repair, 14,575 children age-matched 5% Danish population sample < 16 years-old	No evidence that single anesthetic exposure reduced academic performance at age 16 after adjusting for cofounding factors	Inguinal hernia repair	Test scores at ninth grade, children not attaining test scores
2011	DiMaggio et al	Retrospective cohort study	10,450 siblings 0-3 years-old enrolled in New York State Medicaid program	Children who had surgery had 60% greater risk of diagnosis of developmental and behavioral disorders than siblings who did not	All	Developmental or Behavioral Disorders

2011	Flick et al	Matched cohort study	350 children < 2 years-old exposed to anesthesia, 700 unexposed controls	Exposure to anesthesia < 2 years of age is an independent risk factor for learning disabilities but not interventions related to emotions or behavior	All	Learning disabilities, individual education program for emotional/behav-ioral disorder, group achievement tests
2011	Guerra et al	Single institution study	95 neonates < 6 weeks-of-age	No evidence of association between anesthesia and adverse neuro-developmental outcomes	Congenital heart surgery	Adaptive Behavior Assessment System
2012	Sprung et al	Birth cohort study	5357 children: 341 ADHD cases in children who remained in Rochester, MN after age 5	Children with repeated exposure to GA < 2 years-old have increased risk of ADHD with adjustment for co-morbidities	All	Attention-deficit/hyperactivity disorder
2012	Block et al	Single institution study	577 children under age 1, 58 children with no risk factors	Findings suggest possible adverse effects of anesthesia during infancy on academic achievement	All	Academic achievement tests
2012	Ing et al	Birth cohort study	Analysis of Raine study with 2608 children < 3 years-old; 321 exposed to anesthesia	Anesthesia exposure before age 3 leads to higher relative risk of language and abstract reasoning deficits at age 10	All	Clinical Evaluation of Language Fundamentals, colored progressive matrices
2016	Graham et al	Canadian cohort study	18,056 children: 3,850 exposed to a single GA and 620 exposed to two or more GA, matched to 13,586 non-exposed children in 0-2 or 2-4 years of age	Weak association between multiple GA exposure and long-term neurocognitive impairment	All	Early Developmental Instrument
2016	PANDA study	Multicenter sibling matched cohort study	105 Sibling pairs within 36 months in age; now 8 to 15 years- old	No statistically significant IQ differences in children with a single anesthesia exposure at < 36 months of age	Inguinal Hernia repair	Global IQ, domain-specific neurocognitive functions and behavior

2016	GAS study	International randomized controlled trial	Infants > 26 weeks GA and < 60 weeks PMA (238 children in awake-regional anesthesia group, 294 in GA group)	2-year secondary outcome reveals no evidence that < 1 hour of sevoflurane anesthesia increases risk of adverse neurodevelopmental outcomes 5-year primary outcome pending	Inguinal hernia repair	Primary outcome: Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at age 5 years. Secondary outcome: composite cognitive score of the Bayley Scales of Infant and Toddler Development III, assessed at 2 years.
2018	MASK study	Birth cohort study	997 children completed testing (411, 380, and 206 unexposed, singly exposed, and multiply exposed) respectively	Multiple anesthetic exposures associated with behavioral and learning difficulties	All	Primary outcome: Wechsler Abbreviated Scale of Intelligence Secondary outcome: parent reports and neuro-physiologic assessments
2020	Ing et al	Observational study	42,687 Anesthesia-Exposed children, 213,435 unexposed children < 5 years-old	Children with a single exposure to surgery and anesthesia were 37% more likely than unexposed children to persistently use ADHD medication	pyloromyotomy, inguinal hernia repair, circumcisions outside the perinatal period, and tonsillectomy and/or adenoidectomy	ADHD medication use following anesthesia exposure

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