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Neurotoxic Effects Of Anesthesia On The Developing Brain

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Abstract

Each year, thousands of neonates receive anesthesia and/or sedation for various surgical procedures. With advancements in neonatal care and surgical techniques, the number of infants receiving anesthesia globally will continue to increase. A relatively large and growing body of literature suggests that exposure to general anesthetics can be detrimental to the developing brain. Based upon various animal studies, it is thought that exposure of the immature brain to anesthetic agents may result in apoptosis, neurodegeneration and ultimately long-term cognitive deficiencies (Walters & Paule, 2016). This information presents a dilemma for practitioners when caring for a neonate requiring a surgical procedure, knowing that exposure to the very agents that will alleviate pain, provide adequate sedation and maintain anesthesia, may also result in adverse neurological outcomes. Further compounding this issue, there is currently no known safe alternatives for children undergoing surgery. Although various literature exists suggesting that general anesthesia (GA) has negative effects on neurodevelopment (ND) outcomes, it is unclear as to what extent. It is also unclear as to what other treatments or health related factors during the neonatal period may contribute to long-term outcomes. The following literature review will provide an examination of various retrospective cohort studies as well as one recent randomized controlled trial, all of which sought to determine the association between exposure to GA during the neonatal or early childhood period with ND outcomes. Variations between the reviewed studies include, type of surgical procedure, age and method of ND assessment, and duration of GA. The goal of this review is to provide a description of what is currently known about the effects of GA on the developing brain and what further research is required.

Introduction

Examination of the effects of general anesthesia (GA) on neurodevelopment (ND) has greatly accelerated since various laboratory studies have demonstrated adverse effects on infant rats and other animals. It is hypothesized that neurotoxic effects are potentially mediated through actions that occur at the N-methyl-D-aspartic acid (NMDA) glutamate receptors and/or gaba-aminobutyric acid (GABA) receptors (DiMaggio, Sun, & Li, 2011). More specifically, laboratory evidence has revealed that NMDA receptor antagonists and GABA receptor agonists trigger apoptotic cellular death and neurodegeneration in the immature rat brain (Walters & Paule, 2016). This process is thought to be similar to the effects of ethanol, a well-known teratogenic agent, which can result in fetal alcohol syndrome (FAS). The clinical relevance of animal studies, however, has not been fully determined. When compared to humans, infant rats have a relatively short and vulnerable synaptogenesis period, and relatively high doses of anesthetic agents over long durations have been used in laboratory studies to trigger apoptosis (DiMaggio et al., 2011). This information indicates that in order to extrapolate this evidence to human infants and children, repeated exposure of GA over long periods of time may be necessary.

Neurotoxicity in Rodents

It has been well established in neonatal rodent studies that the blockade of NMDA receptors for a few hours during the brain growth spurt leads to an increase in apoptotic cell death. Original studies demonstrated that NDMA receptors agonists, (+) MK801, phencyclidine (PCP), ketamine, and carboxypiperazin-4-yl-propyl-phosphoric acid (CPP), all induce apoptotic cell death and neurodegeneration in a similar fashion in the postnatal day (PND) 7 rodent brain (Walters & Paule, 2016). Subsequent research extended these findings to GABA receptor

agonists. According to Walters and Paule (2016), research has demonstrated that benzodiazepines, including diazepam and clonazepam, as well as barbiturates such as phenobarbital and pentobarbital, all result in extensive cellular apoptosis in PND 7 rodents. Examination of the critical role that the NMDA and GABA systems play during brain development ultimately demonstrate that these findings are not unexpected. This is because regulation of neuronal survival, migration, axonal and dendritic structure, and synaptogenesis and plasticity are regulated by the L-amino neurotransmitters glutamate and GABA (Walters & Paule, 2016). Given this information, it is not surprising that the disruption of these receptors via anesthetic agents would adversely impact the developing brain.

Many of these findings have not only been replicated, but also extended to a variety of general anesthetics including sevoflurane, isoflurane, N2O, desflurane, propofol, and ketamine. Each of these agents have been shown to result in a similar form of neuronal damage in neonatal rats (Walters & Paule, 2016). Exposure to GA has been shown to disrupt mitochondria integrity and function, impair glial development and function, alter dendritic spine morphology and density, alter synaptic morphology and induce synaptic loss, impair neurogenesis, and inhibit long-term potentiation, all in addition to the typically discussed effects of apoptotic cell death (Walters & Paule, 2016). In summary, these changes have been seen with several different general anesthesia drugs, are greater with increasing exposure, and appear to be less severe in older animals. The anesthetic agents mentioned are often used when providing anesthesia for pediatric and neonatal patients, making it important for anesthesia providers to explore what lasting effects they may produce.

Literature Review

The clinical consequences of this information for anesthesia providers is difficult to determine. Although all anesthetic agents appear to cause neurocognitive harm in animal models, hard evidence that this is true in humans remains somewhat ambiguous. This is due to fact that the majority of studies to date involve retrospective cohorts with various other factors that may influence ND outcomes. Some of these factors include existing co-morbidities, duration of anesthesia, type of surgical procedures and intensive care unit (ICU) stay. A thorough review of the most recent literature will allow the anesthesia provider to develop best practice guidelines as well as guide areas for future research. The majority of these studies are limited in their application for changes in practice due to their retrospective design and the presence of possible confounding factors. However, one recent randomized trial (RCT) will be discussed in conjunction with a review of the most recent retrospective cohort studies.

Available Retrospective Data for General Surgeries

The majority of retrospective studies in existence have suggested at least some relationship between exposure to GA and increased risk for poor ND outcomes. Bong, Allen and Kim (2013) evaluated a cohort of children who received general anesthesia for minor surgery before the age of one. These children were aged-matched with a cohort of children at the same institution who were never exposed to anesthesia. The exposed cohort consisted of American Society of Anesthesiologists (ASA) class I or II pediatric patients who received sevoflurane GA prior to their first birthday. Surgical procedures in this cohort lasted between 30 and 130 minutes. Outcomes were measured at 12 years of age using the following criteria: (1) aggregate scores in the Singapore Primary School Leaving Examination (PSLE) and (2) the presence of a formally diagnosed learning disability compared with children who were never

exposed to anesthesia or sedation. The authors found that there was a 4.5 times greater incidence of a formal diagnosis of learning disabilities by the age of 12 in apparently healthy children who were exposed to GA versus those with no exposure. Study precision, however, was inadequate to detect a clinically relevant difference in PSLE scores.

A similar study was conducted by Ing et al. (2012), which sought to examine the association between the exposure to anesthesia in children under the age of three and outcomes in language, cognitive function, motor skills, and behavior at age 10. The study assessed a cohort of children born in Western Australia from 1989 to 1992. Of this cohort, 321 were exposed to GA before the age of three, while 287 were unexposed. Cognition was assessed by using the Symbol Digit Modality Test (SDMT) and the Raven's Colored Progressive Matrices (CPM). The SDMT assessed visual tracking, attention, and motor skills, and generated an oral and written score, while the CPM measured global cognitive performance, nonverbal intelligence and visuospatial functions. The results demonstrated that GA exposed children had lower scores than their unexposed peers in receptive and expressive language. Cognition scores measured by the CPM were also significantly lower in the GA group. In this study, there was no direct access to medical records and children were classified based upon whether or not they had a surgical procedure prior to the age of three. The authors admit that the lack of detailed anesthetic records limited their ability to differentiate between the type of GA utilized as well as the length of exposure. This is important to note because many studies have shown a higher incidence of poor ND outcomes with increasing exposure time.

DiMaggio et al. (2010) specifically examined a cohort of children under the age of three exposed to anesthesia for hernia repair. The cohort involved children who were born in New York between 1999 and 2001 and were covered under the Medicaid system. It was found that

these patients had more than two times the risk of a receiving a developmental or behavioral disorder when compared to their age-matched counterparts. The researchers analyzed data using the Cox proportional hazards model controlling for age, gender, race and presence or absence of any complicating birth related diagnosis. DiMaggio, Sun and Li (2011) preformed a follow-up study in which they evaluated for the incidence of cognitive and behavioral disorders, in the same cohort described above, compared to a sibling-matched cohort. Siblings who were exposed to GA had a greater than 60% increased risk of ND disorders. Additionally, the incidence of cognitive and behavioral disorders was directly related to the number of surgical and anesthetic exposures.

Wilder et al. (2009) conducted a study to assess the association between anesthetic exposure before the age of four and the development of reading, written language, and math learning disabilities. The study involved a cohort of children born in Minnesota between 1976 and 1982. After exclusion criteria was considered, the final cohort consisted of 5,357 children. Of this cohort, 593 received GA prior to the age of four. Wilder and colleagues argued that if exposure to GA significantly impacts ND outcomes, there should be a correlation between dose and/or length of exposure and relevant outcomes. According to the authors, a solitary exposure to GA carried no increased risk for developing a learning disability. However, children in the groups who received two anesthetics and three or more anesthetics were found to be at increased risk for developing a learning disability. Additionally, longer durations of GA resulted in an increased risk for learning disabilities, reaching statistical significance at a duration of 120 minutes or longer.

Sprung et al. (2012) assessed the same cohort as Wilder et al. (2009), but looked specifically at the development of attention deficit/hyperactivity disorder (ADHD) in children

exposed to GA prior to the age of two years. Cases of ADHD diagnosed prior to age 19 were identified. Similar to the study performed by DiMaggio et al. (2010), the Cox proportional hazards regression model was used to assess exposure to procedures requiring general anesthesia as a predictor of ADHD using a stratified analysis with strata based on a propensity score including comorbid health conditions. The cohort was divided into three groups depending upon their exposure to anesthesia to include, none, one, and two or more exposures. The authors report that 341 cases of ADHD were identified. For children with no postnatal exposure to GA prior to the age of two, the cumulative incidence of ADHD was 7.3%. For one and two or more exposures, the incidence was 10.7%. Ultimately, the researchers concluded that repeated exposure to surgical procedures requiring general anesthesia prior to the age of two is associated with an increased risk of developing ADHD.

Exploration of these retrospective studies suggests a strong association between exposure of the immature human brain to anesthesia for general surgeries and cognitive or behavioral issues. In all cases that report length and number of exposures, the effects appear to be dose-related, increasing in occurrence with multiple anesthetic exposures. It is important to note, however, that these studies are limited due to their retrospective design and inability to rule out various confounding factors. For example, it is not clear what effects surgical stimulus, other health conditions and specific age at time of exposure may have on ND outcomes. It is possible that the physiological stress of the procedure itself could result in neurodegeneration. According to Sprung et al. (2012), there is accumulating evidence suggesting that insults in the perinatal and postnatal period, including stress and inflammation, may be correlated with an increased incidence of poor ND outcomes.

Additionally, the anesthetic type and length of exposure in the above studies differ. The first study discussed by Bong, Allen and Kim (2013) included GA with sevoflurane as the primary anesthetic, while in Wilder et al. (2009) and Sprung et al.'s (2012) studies, 88% of the anesthetics included halothane and some anesthetics included nitrous oxide. The remaining studies did not report a specific anesthetic agent utilized. It becomes challenging to interpret these results as it does not necessarily reflect current practice or the difference between various types of anesthetics. Ultimately, this information supports the importance of pursuing randomized clinical trials to determine to what extent GA effects the immature human brain and whether causality can be attributed to other factors.

Complex Cardiac Surgeries and Anesthesia

In addition to retrospective studies examining the effects of GA on infants and children undergoing general surgery, there are various studies that have looked at infants receiving anesthesia for surgery for congenital heart diseases (CHD). In Europe, Asia, and North America CHD is present in seven to nine per 1,000 births, and approximately 25% require surgery in the first year of life (Andropoulos et al., 2014). Additionally, problems with general intelligence, receptive and expressive language, and gross and fine motor functioning occur in 30-50% of neonates undergoing complex cardiac surgery. Unfortunately, it is unclear as to which factors have the greatest effect on ND outcomes in this patient population. Possible factors in addition to GA expousre include, but are not limited to, structural brain immaturity, chromosome anomalies, magnetic resonance imaging (MRI) brain injury, prolonged deep hypothermic circulatory arrest, extreme hemo-dilution during cardiac bypass and ICU length of stay. Since many of these factors are non-modifiable, it is desirable for research to determine the extent to which GA

effects ND outcomes in this patient population and in what ways, if any, anesthetic modalities may be modified.

Andropoulos et al. (2014) preformed a retrospective study to determine the association of perioperative anesthetic exposure with ND outcomes at the age of 12 months in neonates undergoing complex cardiac surgery. All subjects were less than 30 days old and scheduled for surgery with hypothermic cardiopulmonary bypass (CPB) for greater than 60 minutes. The anesthesia technique for all patients consisted of isoflurane, fentanyl, and midazolam. The cohort had a mean volatile anesthetics (VAA) exposure of four minimum alveolar concentration (MAC) hours in the first year of life with a range of <0.5 to 15 MAC hours. ND testing was performed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Multiple covariates were first assessed by a linear regression analysis. These covariates included things such as birth weight, gestational age, total ICU and hospital length of stay, maternal IQ and type of cardiac lesion. The results demonstrated an association between VAA, ICU length of stay, brain injury and poor ND outcomes at 12 months of age. According to the authors, increasing VAA exposure resulted in a significant association with lower cognitive scores after adjusting for various relevant covariates, however, ICU length of stay was most strongly associated with poor ND outcomes. Of note, exposure in this cohort took place, specifically, in the neonatal period, which is the time of the most rapid synaptogenesis and brain growth in humans.

A similar study was completed by Diaz et al. (2016) to determine the relationship between exposure to VAA and ND outcomes in patients with hypoplastic left heart syndrome (HLHS). The cohort consisted of infants six months of age or younger undergoing cardiac surgery with CPB. Initial cardiac surgical intervention in 98% of the cohort took place in the neonatal period. All patients underwent additional cardiac and/or non-cardiac procedures post

initial surgery. The type of VAA used for patients varied, with exposures ranging from 0-35.5 MAC hours. The Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) was utilized to asses ND outcomes between four and five years of age. Testing included full scale IQ, verbal IQ, performance IQ and processing speed. Results, once again, demonstrated that greater exposure to VAA, after adjusting for multiple covariates previously shown to impact ND outcomes, resulted in worse neurological outcomes in this patient population.

Both studies suggest that anesthesia exposure may be a modifiable risk factor, specifically in a patient population that is already at risk for poor neurocognitive outcomes due to other non-modifiable factors. However, there are various limitations that should be noted. Both studies are retrospective in their assessment of anesthetic exposure. In both studies, researchers admit that anesthetic exposure may have been under or over-estimated due to various types of recordkeeping and handwritten records. Additionally, longer hospital length of stay was strongly associated with poor ND outcomes. Many patients that fit into the category of increased hospital length of stay also had additional surgeries requiring more exposure to anesthesia. Although the authors attempted to control for this by adjusting for length of stay, the precise effect of each factor is difficult to determine.

Randomized Controlled Trial

All of the previously mentioned studies have demonstrated some association between anesthesia exposure to the developing brain and poor ND outcomes. However, due to confounding factors, exact causation cannot be established or excluded. For this reason, RCTs can provide more definitive answers for anesthesia providers.

The first and only RCT to date addressing this issue was completed by Davidson et al. (2016). As with previous studies, the authors set out to establish whether GA in infancy has any

correlation with poor ND outcomes. In this study known as, *General Anesthesia Compared to Spinal Anesthesia* (GAS) *trial*, they report the secondary outcome of ND outcomes at two years of age in a GA group compared to an awake-regional anesthesia group. Infants younger than 60 weeks post conceptual age, born greater than 26 weeks gestation, and who had inguinal herniorrhaphy were randomly assigned to one of the two groups. The awake-regional anesthesia group received either a spinal anesthetic or a caudal anesthetic, while the GA group received sevoflurane and a mix of air and oxygen. Eligible infants were recruited from 28 hospitals in Australia, Italy, the USA, the UK, Canada, the Netherlands, and New Zealand. Exclusion criteria included any contradiction with either anesthetic technique, history of CHD requiring surgery or pharmacological treatment, mechanical ventilation immediately before surgery, chromosomal abnormalities or other known congenital anomalies that might affect neurodevelopment, previous exposure to VAAs or benzodiazepines as a neonate or in the third trimester in-utero, any known neurological injury such as cystic periventricular leukomalacia or grade three of four intraventricular hemorrhage, any social or geographical factor that might complicate follow up, or having a primary language at home in a region where ND tests are not available in that particular language.

In the awake-regional group the decision between a caudal anesthetic or combined spinal-caudal was determined by the institutions protocol. Spinal anesthesia consisted of 0.2 mL/kg of 0.5% isobaric bupivacaine with a minimum volume of 0.5 mL. In the USA and UK other agents were used due to lack of availability of isobaric bupivacaine. In the USA 0.13 mL/kg of hyperbaric 0.75% bupivacaine, and in the UK 0.2 mL/kg of 0.5% levobupivicaine was used. Caudal anesthetics consisted of total doses of up to 2.5 mg/kg of 0.25% bupivacaine or in the UK, 0.25% levobupivicaine. In the USA if the surgery was likely to last greater than one hour,

patients were given a loading dose of 3% chloroprocaine. This was given via a caudal cannula in 1 mL/kg divided doses to total no more than 0.25 mL/kg per 15 seconds and then an infusion of 1-2 mL/kg per hour. In this group, oral sucrose was utilized to settle the child if needed but all other forms of sedation were avoided. If awake-regional anesthesia was ineffective and conversion to GA was required, the patient was then excluded from the study.

A sevoflurane induction was utilized in the GA group. Anesthesia was maintained with sevoflurane in a mix of air and oxygen with the concentration being left to the discretion of the anesthesia provider. The choice of airway management, ventilation technique, and use of neuromuscular blockers varied and again were left to the discretion of the provider. Nitrous oxide and opioids were not allowed, however a caudal, ilioinguinal-iliohypogastric or field blocks with bupivacaine could be done in both groups for post-operative pain management. Oral or intravenous acetaminophen was also allowed.

The primary outcome of the GAS study will be the WPPSI-III score at five years of age and results should be known after 2018. The secondary outcome, reported in this study, is the Bayley-III, assessed at two years of age. The Bayley-III assessed cognitive, language, and motor levels. Using this outcome, the authors found no evidence that less than one hour of sevoflurane anesthesia in infancy increases the risk of neurocognitive dysfunction at two years of age when compared to awake-regional anesthesia. The median sevoflurane exposure in this study was 54 minutes. The authors argue that this evidence demonstrating equivalence between awake-regional anesthesia and GA during infancy in terms of ND outcomes, may support the fact that results of previous studies are due to the many confounding factors. They do, however, acknowledge that the short exposure studied here does not rule out the possibility that anesthetics may lead to adverse ND outcomes with increasing exposure.

Discussion

General anesthetics have been shown to have adverse neurocognitive outcomes in preclinical animal studies, creating great concern for the effects of anesthetic exposure on the developing human brain. A thorough literature review reveals that this concern is not unwarranted. Various retrospective studies have found an association between anesthesia exposure in early childhood and poor ND outcomes, however, it is difficult to discern the exact causality of neurocognitive dysfunction in many of these studies. Poor outcomes could also be explained by many other variables such as the physiological stress of surgery, comorbid health conditions or prolonged ICU stay. In many of these patient populations, specifically for patients undergoing complex cardiac surgeries, it would be unethical to preform RCT in which one group is assigned to not receive a general anesthetic. For this reason, it is very difficult to determine to what extent modification of GA may improve ND outcomes.

The recent RCT by Davidson et al. (2016) is the first study of its kind and provides strong evidence that exposure of less than one hour of sevoflurane does not increase the risk of poor ND outcomes at two years of age. When comparing this data to other studies it is important to note that many of the studies supporting poor ND outcomes involved much greater exposure time to GA. Additionally, it is important that the children in the GAS study are assessed later in life to determine the long-term effects on neurocognitive development. Although this trial is the strongest clinical evidence to date that general anesthesia may not result in neurotoxicity, more RCTs with greater exposure and further follow-up are required for definitive answers. In 2018 the primary outcome of the GAS study will be known and will be very helpful in guiding further research.

As an anesthesia provider, it is important to consider what this incomplete evidence means for current practice. It is very challenging, however, to provide specific recommendations given the lack of conclusive evidence and RCTs. The US Food and Drug Administration (FDA) and the International Anesthesia Research Society (IARS) have created a partnership, SMARTTOTS, which has established various recommendations that are recognized by many pediatric and anesthesia bodies (Davidson, 2016). The recommendations, however, lack specificity and essentially suggest that any unnecessary anesthesia should be avoided. The SMARTTOTS partnership explains that it is not yet possible to discern whether GA is safe for children or neonates, even in a single and short duration. They argue that each anesthetic should be considered on a case-to-case basis and ultimately the risk of exposure to GA should be weighed against the potential harms of delaying or canceling a surgical procedure.

Conclusion

Although it is clear that anesthetic agents result in neurotoxicity in neonatal rodents, it has not yet been determined as to what extent this can be generalized to the neonatal human brain. Establishing a cause and effect relationship is extremely difficult when there are multiple variables that cannot be controlled due to ethical reasons. Two goals have been defined by the 2011 IARS SmartTots session. These goals include refining our understanding of anesthetic-induced neurotoxicity at a cellular level and improving our understanding of anesthesia-related behavioral and neurodevelopmental sequelae in mammalian species exposed to anesthesia during the critical periods of brain development (Chiao & Zuo, 2014). As anesthesia providers continue to search for definitive answers and guidelines, it is imperative to inform parents of not only what information is known but also what remains unknown. The research published thus far has not been significant enough to trigger any substantial clinical change for anesthesia providers.

The primary results of the GAS trial may be telling and will hopefully provide insight into what steps should be taken next. In the meantime, it is important to continue to expand research efforts for human trials while remaining educated and advocating for this venerable population.

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