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CLINICAL EVIDENCE OF EFFECT OF GENERAL ANESTHESIA ON DEVELOPING BRAIN OF A CHILD. A SCOPING REVIEW

Suhael Ahmed
College of medicine and dentistry, Riyadh Elm University, Riyadh, Saudi Arabia

Faisal Abdullah Alharbi
King Saud University, Riyadh, Saudi Arabia

Sara Mazen Fahad Alomran
Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia.

Hayat Alowais
College of medicine and dentistry, Riyadh Elm University, Riyadh, Saudi Arabia.

Norah Abdulrahman Alobaid
Majmaah University, Majmaah, Saudi Arabia

Reem Abdullah Sulaiman Alnutayfi
Majmaah University, Majmaah, Saudi Arabia

Maram Fahaid M Al Hemaidani
College of Dentistry, Mustaqbal University, Qassim, Saudi Arabia

Shatha Saad Alasmary
King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Renad Mohammed Al-Ibrahim
College of Dentistry, King Khaled university, Abha, Saudi arabia

Norah Saleh Alghuwainem
King saud University, Riyadh, Saudi arabia

Reoof Mohammed Alotaibi
Majmaah university, Majmaah, Saudi arabia

Ahmed Abdulrahman Ali Alghamdi
Al Baha University, Al Baha, Saudi Arabia

Owais AlGhamdi
Al Baha University, Al Baha, Saudi Arabia

Abstract

In recent years, the potential ramifications of general anesthesia on the developing brain of a child have garnered attention and concern within the medical community. With growing evidence and ongoing research, this topic explores the clinical findings surrounding the effects of general anesthesia on the neurodevelopment of children, shedding light on the long-term consequences and potential strategies to mitigate any adverse effects. Exposure to general anesthesia in early infancy may result in neurocognitive deficits and learning disabilities in adulthood, according to a number of studies. The prolonged and repetitive administration of anesthesia may disrupt the normal synaptic development and neuronal activity in the developing brain, potentially impairing cognitive functions. To minimize the risks associated with general anesthesia, medical professionals are now exploring alternative techniques such as regional anesthesia and conscious sedation to limit the exposure of developing brains to anesthesia drugs. The effects of general anesthesia on the maturation of the brain are the subject of this review.

Keywords- child, pediatric anesthesia, neurodevelopment

Introduction

General anesthesia is commonly used by pediatric patients for various surgical procedures. However, recent research has elicited apprehension regarding the possible ramifications of anesthesia on the nascent brain. A critical period of brain development is particularly susceptible to external influences; therefore, anesthesia exposure during this time may interfere with normal neurodevelopmental processes. It is imperative to comprehend the potential ramifications of anesthesia on the development of the pediatric brain in order to safeguard the health and safety of young patients..

General anesthesia for pediatric patients has been associated with a range of potential risks. Studies have suggested that exposure to anesthesia during early childhood may be associated with an increased risk of learning disabilities, attention deficit hyperactivity disorder (ADHD), and neurodevelopmental disorders. Additionally, some research has indicated a potential link between anesthesia and cognitive impairments, such as decreased IQ scores and memory problems. Understanding these potential risks is crucial for developing strategies to minimize harm and optimize patient outcomes.

Animal experiments conducted in recent years have yielded empirical support for the neurotoxic properties of anesthetics, which manifest as enduring cognitive impairments (Liu et al., 2020; Guo et al., 2023). At the extremities of age, these toxic effects are most pronounced in neonates and preterm infants, as well as aged animals. The investigation into the identification of potential mechanisms is ongoing at this time. Researchers across the world have undertaken several retrospective studies to gain a more comprehensive understanding of the potential neurotoxic impacts on the human brain of neonates and young children. This article examines the current clinical data, the potential transfer of experimental data to humans, and the current literature concerning the effect of general anesthesia on developing brains.

Search strategy

We identified the articles included in this review through PubMed, Web of Science, and Scopus databases using the keywords "neurotoxicity," "children," and "pediatric" with "anesthesia." This search returned a total of 152 results. After removing review articles (40), investigations into complications related to anesthesia other than those involving local anesthetics (40), and studies that did not involve humans (18), we conducted a quality check on the remaining primary studies.

Discussion

Critical periods of brain development in children

During the early weeks and months of pregnancy, the ectoderm establishes the foundations of physiological brain development through the fissure and neural plate. The fissure and neural plate originate in the ectoderm. By the conclusion of the third month of gestation, vigorous cell division and migration form the five vesicles. These vesicles give rise to the cerebrum, cerebellum, diencephalon, and brainstem. The brain contains approximately 125,000 cells at that time (Cowan et al., 1979). Upon delivery, the brain increases the quantity of neurons to one billion, generating an estimated two hundred and fifty thousand neurons via cell division each minute (Cowan et al., 1979). A multitude of neurons, particularly those that do not form synaptic connections, perish during brain development via programmed cell death, also known as apoptosis (LaMantia et al., 2024; Bourgeois et al.,1997). The process of synaptogenesis begins during the last trimester of pregnancy and concludes by the end of the second or third year of an individual's life (Sowell., 2003). Several elements are crucial in the development, movement, specialization, and formation of connections between neurons. Activation of the excitatory GABA receptor in a young brain causes the neuron to depolarize because of the increased concentration of chloride inside the cell. During development, the concentration of chloride inside cells drops, and the GABA receptor undergoes a transformation from being excitatory to being the primary inhibitory receptor in the adult brain (Nguyen et al., 2001; Herlenius et al., 2004). Other crucial components involved in the process of neurogenesis include growth factors, including nerve growth factor and brain-derived

neurotrophic factor (BDNF). These factors primarily govern neuronal survival, axogenesis, and dendritic differentiation from progenitor cells (Forray et al., 2016).

Potential risks associated with general anesthesia in pediatric patients

Consuming a range of substances, including alcohol, benzodiazepines, and antiepileptic medication, during pregnancy widely recognizes that it results in deleterious effects on the developing fetus (Iqbal et al., 2002; Jones et al., 2010). Fetal alcohol syndrome is an adverse outcome of alcohol consumption during pregnancy, manifesting as microcephalus, epileptic convulsions, behavioral irregularities, and cognitive impairments. Administering anesthesia, surgery, or intensive care treatment, including sedation, simultaneously can induce behavioral abnormalities in children (Jones et al., 2010). Adverse effects, such as inadequate pain therapy, absence of premedication, or withdrawal symptoms, are primarily ascribed to the circumstances. Over the past decade, an abundance of data published from animal studies has prompted extensive retrospective studies in humans. Researchers examined whether anesthesia exposure during the first three to four years of life, which corresponds to the human brain development phase, correlates with adult learning and behavior abnormalities. Researchers compiled the information for the studies from various birth registries or cohorts in the United States, Australia, or Europe (Xiao et al., 2022).

Wilder et al. (2009) utilized a cohort of Minnesotan children born between 1976 and 1982 to address a number of inquiries concerning anesthetic exposure and cognitive disabilities. The effect of general anesthesia during a caesarean section on brain development is one area of inquiry. Caesarean section was performed on 497 out of the over 5,300 infants in this cohort. 193 mothers underwent regional anesthesia, and 304 received general anesthesia. There was no discernible disparity in the later occurrence of cognitive disabilities among the groups, according to the study (Wilder et al., 2009). The authors examined whether the exposure of newborns or infants to anesthetics is linked to the occurrence of cognitive impairments. The authors performed a retrospective analysis on a cohort of more than 593 children who underwent general anesthesia before the age of four years. Either a total anesthetic duration exceeding 120 minutes or two or more instances of exposure to anesthesia significantly linked to the occurrence of learning deficits (Wilder et al., 2009). Di Maggio et al. conducted a study using Med-Icaid data to examine the occurrence of herniotomy, a frequently performed surgical operation on young children. The study focused on a cohort of children born in New York between 1999 and 2001 (DiMaggio et al., 2009). The researchers examined the association between anesthesia exposure during inguinal hernia repair in three-year-olds and the occurrence of learning disabilities. Contrary to the findings of Wilder et al., the incidence of cognitive disabilities increased by 2 to 3-fold following a single anesthetic exposure. Girls were less affected than boys. Unfortunately, the authors did not specify the medications used or whether regional anesthesia was utilized. Another study that investigated the correlation between solitary anesthetic exposure during the first three years of life and neurocognitive development by the age of ten reported comparable outcomes. Researchers

observed a significant decline in the children's performance in language and abstract reasoning (Sun et al., 2016). On the contrary, a number of European studies have failed to establish any correlation between early childhood anesthesia exposure and the occurrence of cognitive disabilities or behavioral abnormalities. A Danish study enrolled infants who required uterine hernia repair within the first year of life. There was no statistically significant difference in the academic performance of both groups on a ninth-grade standardized test administered by a nationwide school district. Exploiting twin research has the potential to eliminate genetic variations. Researchers retrospectively examined the Dutch Twin Registry, comparing monozygotic twins under the age of three, and administering general anesthesia to one twin. Researchers found no discernible distinction in the prevalence of cognitive disabilities between the exposed twins and the non-exposed twins (Hansen et al., 2011). Researchers have conducted numerous retrospective clinical trials in recent years to examine the correlation between early anesthesia exposure and neurocognitive outcomes. Nevertheless, the results fail to offer conclusive evidence, and the discourse surrounding the significance of retrospective data persists. Cohort studies, as opposed to randomized controlled trials, encompass extensive and heterogeneous populations. It is essential to account for confounding variables through critical and complex adjustment analysis, and comprehensive patient data is a prerequisite for dependable results. However, as long as all other variables remain unchanged, retrospective studies can identify rare or subtle adverse events related to medications or procedures. All three types of research—randomised controlled trials, retrospective studies, and prospective studies—could provide insights into addressing these scientific inquiries, given the potential for alternative etiologies of neurodegeneration, such as systemic inflammation or cell damage induced by surgical procedures, individual predisposition, co-morbidities, hemostatics, and anesthetic-induced imbalances.

Possible neurodevelopmental consequences of exposure to general anesthesia in children

Wilder et al. (2009) published the first extensive retrospective investigation of anesthetic exposure in children younger than four years old. The study examined the prevalence of subsequent behavioral, cognitive, or developmental difficulties during the school-age years. Subjects exposed to anesthesia for an extended period of time or on multiple occasions had approximately twofold higher rates of problem identification compared to those without any anesthesia exposure. Since then, several retrospective studies have been published, yielding inconclusive findings regarding the correlation between anesthetic exposure and subsequent neurobehavioral and developmental difficulties (Ko et al., 2014; Chemaly et al., 2014). Research conducted in Europe, utilizing standardized academic testing during school years to diagnose learning difficulties, has generally found no correlation between anesthetic exposure and the aforementioned difficulties. The Raine Cohort research conducted in Western Australia included direct formal neurodevelopmental testing and found that individuals exposed to the condition were more susceptible to language impairments (Dontje et al., 2019). Stratmann et al. (2014) conducted a study where they administered a specific recognition memory test to children between the ages of 6 and 11 after they received a dose of 100 of general anesthesia. The researchers considered a difference of five

points between the groups to be statistically significant (Stratmann et al., 2014). In a study conducted by Nishijima et al., the Bayley-III scores for the linguistic, motor, and cognitive domains were nearly indistinguishable between groups at the age of two. The PANDA Study (Pediatric Anesthesia NeuroDevelopment Assessment) involved 105 pairs of siblings, where one sibling had previously undergone inguinal hernia repair under anesthesia at least three years ago (Nishijima et al., 2022). The primary outcome consisted of performance, verbal, and full-scale IQs. The scores in the different categories were practically indistinguishable in these results. Secondary evaluations of memory, language, attention, and executive function measures showed no significant differences. While there were minor discrepancies in the responses of parents on the behavior questionnaire, Both studies imply that there is no association between a single, relatively short exposure to anesthesia and a higher occurrence of negative effects on neurobehavior.

Limitations and gaps in knowledge regarding these effects

While there have been several clinical studies examining the effects of general anesthesia on the developing brain, it is important to acknowledge the limitations of these studies. Many of the existing studies have relied on retrospective data or animal models, which may not fully capture the complexity of the human brain. Furthermore, the challenges of conducting long-term follow-up studies have hindered a comprehensive understanding of the long-term effects of anesthesia exposure in pediatric patients. Recognizing these limitations is essential for guiding future research and informing clinical practice. While some studies have suggested a potential link between general anesthesia and neurodevelopmental effects, there is still ongoing debate and controversy in this field. The scientific community has not fully understood the exact mechanisms by which anesthesia may impact brain development. Furthermore, the long-term cognitive and behavioral outcomes of anesthesia exposure in pediatric patients remain uncertain, with conflicting findings from different studies. Addressing these controversies and knowledge gaps is crucial for advancing our understanding and ensuring the safety of pediatric patients.

Future prospects

More high-quality human studies are needed to determine whether anesthetics directly affect neurodevelopment, particularly in children who have undergone repeated or extensive exposure to anesthesia. These should ideally be randomized trials contrasting anesthesia regimens that induce the changes observed in preclinical studies and those that do not, utilizing healthy neonates. The execution of these proceedings would not be easy. Developing various guidelines and protocols is necessary to minimize the potential harmful effects of general anesthesia. These include preoperative screening to identify patients at higher risk, the use of regional anesthesia techniques whenever possible, and the optimization of perioperative care to minimize the duration and depth of anesthesia. Ongoing research focuses on developing new anesthetic agents and techniques that may cause less harm to pediatric brain development. These strategies demonstrate the commitment

of the medical community to prioritizing patient safety and promoting optimal neurodevelopmental outcomes.

CONCLUSION

The issue of anesthetic neurotoxicity in neonates, young infants, and fetuses is of the utmost importance in the field of pediatric and fetal anesthesia. Due to the exceptionally swift progression of the fetal brain, this demographic may be particularly susceptible to neurodevelopmental risks. There is inconclusive evidence from human studies regarding the relationship between early childhood anesthesia exposure and later deficits in a variety of neurodevelopmental outcomes. Perceived additional risk is minimal. Given the brief exposures and wide range of populations and outcomes involved in preclinical data, inconsistencies with the observed variations in outcomes and generally minor disparities in human studies are expected. Because most of these studies are cohort studies, there is a high chance that other factors will affect the results. This means that any evidence from humans that anesthesia leads to these bad outcomes is very weak. Therefore, recommendations for practice modification, including the FDA warning, remain predominately influenced by preclinical evidence. On the contrary, more robust evidence from human subjects indicates that a brief solitary exposure does not result in adverse neurodevelopmental outcomes for healthy infants.

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