

The Intersection of Anesthesia and Neurotoxicity in the Pediatric Population: Implications for Pediatric Care and Neurodevelopmental Outcomes

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ARTICLE INFO

Received: 📅 October 03, 2024

Published: 📅 October 15, 2024

Citation: Rimsha Bint-e-Hina, Rimsha Malik Zaman, Alina Ansar, Anees Fatima and Urooba Shahab . Problematic Hospital Architecture: Ensuring the Stable Operation of Wireless Communication. Biomed J Sci & Tech Res 59(1)-2024. BJSTR. MS.ID.009247.

ABSTRACT

The potential for anaesthetic-induced neurotoxicity in pediatric patients has become a pressing concern within the field of anesthesiology. Extensive animal studies and clinical trials suggest a link between early childhood exposure to general anaesthesia and subsequent neurocognitive deficits, behavioural alterations, and increased susceptibility to neurodevelopmental disorders. This comprehensive review delves into the underlying mechanisms of neurotoxicity, identifies vulnerable populations, and examines the cumulative effects of anaesthesia exposure. While clinical trials yield mixed results, evidence indicates that single exposures may not significantly impact long-term neurocognitive development. Investigational treatments, including alternative anaesthetic agents such as xenon and dexmedetomidine, demonstrate potential neuroprotective effects. Further research is imperative to inform evidence-based pediatric care and ensure the safe administration of anaesthesia to vulnerable populations.

Keywords: Pediatric Anaesthesia; Neurotoxicity; Neurodevelopmental Disorders; General Anaesthesia; Sedation; Neuroprotection

Abbreviations: ERK: Extracellular Signal-Regulated Protein Kinase; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; ED: emergence delirium; DEX: Xenon and Dexmedetomidine

Introduction

The risk of anesthetic-induced neurotoxicity is considered one of the most significant clinical and research challenges in pediatric anesthesiology [1]. Neurotoxicity refers to the adverse effects of chemical substances on the structure or function of the nervous system, either through direct interaction with neural cells or by disrupting metabolic processes critical to neural function [2]. In the last 15 years, animal studies have increasingly demonstrated the potential for commonly used anaesthetics and sedatives to trigger neuroapoptosis and other neurodegenerative alterations in the developing mammalian brain [3]. Anaesthetic exposure is common, with one in seven children undergoing anaesthesia before the age of three, and those with a history of prematurity or low birth weight have an increased likelihood of repeated exposure [4]. General anesthesia has been unequivocally associated with abnormal central nervous system development, leading to neurocognitive deficits. These findings have raised concerns

regarding the potential for anesthetic-induced neurotoxicity in pediatric patients. A range of behavioural changes has been observed in children following exposure to general anaesthesia, including the emergence of delirium, which may serve as a clinical manifestation of such neurotoxicity [5]. These findings underscore the need for continued research into the safety and long-term effects of anaesthetic exposure in pediatric populations.

Mechanism of Neurotoxicity

Anesthesia-induced neurotoxicity, particularly in the developing brain, has become a growing concern. Recent studies have identified several mechanisms through which anaesthetics can damage neurons and impair cognitive function. Synaptogenesis, the formation of new synapses, is particularly vulnerable to anesthetic-induced damage. Different brain regions undergo synaptogenesis at different times, making them susceptible to injury at specific developmental stages

[6,7]. The frequency and duration of anaesthetic exposure are significant factors. Higher cumulative anaesthetic doses can increase the risk of neurotoxicity. While the mechanisms of neurotoxicity are similar across various anaesthetics, the specific drug used may influence the severity of damage [8]. Anaesthetics may interfere with neurogenesis, the process of generating new neurons. This can impair the brain's ability to repair and regenerate itself. Isoflurane-induced loss of stem cells and reduction of neurogenesis occurred in young but not in adult brains [9]. Anaesthetics can affect the balance of GABAergic neurotransmission, which is crucial for brain development. Changes in GABAergic signalling can disrupt the normal excitatory-inhibitory balance and contribute to neuronal damage [10]. Anaesthetics such as Volatile anaesthetics, propofol, barbiturates and benzodiazepine act as agonists of the GABA receptor [11]. In the developing brain, activation of GABA receptors can lead to depolarization.

As a result, the depolarization-induced increase in intracellular calcium concentration can reach levels detrimental to the cell and may trigger apoptosis [12]. Many anaesthetics are antagonists of the NMDA receptors. Inhibition of NMDA receptor signalling during the critical period of synaptogenesis can lead to excitotoxic neurodegeneration and neuronal suicide (apoptosis). Numerous agents implicated in neurodegeneration function as NMDA receptor antagonists, including ketamine, nitrous oxide and ethanol [13]. Suppression of prosurvival signalling pathways such as those involving phosphorylated extracellular signal-regulated kinase $\frac{1}{2}$ (ERK1/2) and kinase (Akt) by ketamine and propofol can lead to neuroapoptosis. Ethanol-induced neuroapoptosis is preceded by suppressed phosphorylation of extracellular signal-regulated protein kinase (ERK) [14]. Anaesthetics can also interfere with the development of dendritic spines, which are important for synaptic transmission. This can lead to changes in neural circuitry and potentially impair cognitive function [15].

Risk Factors and Vulnerable Populations

Relationship with Frequency of Exposure

Research examining the correlation between exposure frequency and neurological outcomes reveals concerning patterns. While two-thirds of single-exposure studies found no adverse correlation, multiple-exposure studies consistently reported significant neurological declines. A comprehensive review of 27 studies on exposure frequency and risk yielded mixed results, with 14 reporting equivalent outcomes, eight finding increased harm, six observing no effect, and 13 demonstrating exacerbated harm with repeated exposures. Notably, seven studies linked multiple exposures to more severe adverse outcomes, suggesting a cumulative effect [16].

Age-Related Effect

Ing, et al. (2019) examined neurodevelopmental outcomes following anaesthesia exposure in children aged 3-10. Their retrospective analysis revealed distinct vulnerability windows for various cognitive domains.

- Children exposed to anaesthesia after age 3 showed deficits in gross and fine motor skills, whereas language and abstract cognition remained intact.
- Younger children (<3 years) exhibited cognitive and socio-affective deficits.
- Specific functional domains exhibit unique vulnerability windows [17].

A review of 66 studies investigating the neurocognitive effects of general anaesthesia in children revealed significant concerns. Specifically, 65.2% of studies involving children under seven detected adverse neurocognitive effects, with neonates and infants exhibiting heightened vulnerability. The majority of studies utilized three years as the age threshold, balancing vulnerability with statistical analysis requirements. Older children, aged 7-18, were examined in six studies, with 83.33% reporting neurological impairment. Subgroup analysis by age yielded mixed results, with four studies indicating increased vulnerability in younger children, 11 finding no distinction, and three suggesting older children were more susceptible [16].

Clinical Trials

1. GAS Trial (2019): A randomized controlled trial (n = 722) compared awake-regional anaesthesia to sevoflurane-based general anaesthesia for inguinal hernia repair in infants (<60 weeks post-menstrual age). No significant difference in full-scale IQ at 5 years was found [16].
2. MASK Study (2018): A propensity-matched cohort study (n = 998) examined anaesthesia exposure (<3 years) and neuropsychological outcomes (8-20 years). No significant differences in full-scale IQ or most secondary outcomes were observed between singly exposed and unexposed children [16].
3. Sibling Study (2015): A sibling-pair study (n = 105) investigated general anaesthesia exposure (<36 months) and neurocognitive outcomes (8-15 years). No significant differences in global cognitive function, domain-specific functions, or behaviour were found [16].

These studies provide evidence suggesting that single exposures to general anaesthesia in early childhood may not significantly impact long-term neurocognitive development [16].

Emergence Delirium Post Anesthesia

Emergence delirium is a transient post-anesthetic complication characterized by a dissociated mental state, marked by agitation, inconsolability, irritability, and uncooperativeness, typically resolving within 10-30 minutes in pediatric patients. The incidence of emergence delirium varies significantly, affecting 5-10% of adults and up to 80% of certain pediatric populations, with a notable predilection for children under 5 and adults over 65. [18].

General Anesthesia and Psychiatry

Recent evidence suggests that early life exposure to general anaesthesia may constitute an environmental risk factor contributing to the development of neurodevelopmental pathologies. Epidemiological investigations have yielded associations between early life anaesthesia exposure and an increased risk of developing attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), although the latter findings are not universally consistent. Furthermore, the cumulative evidence supporting the contribution of early-life anaesthesia to developmental psychiatric diseases remains tentative [19].

Clinical Manifestations and Long-term Consequences

Propofol use in children for extended sedation has been linked to adverse neurological effects, such as impaired motor function, blindness, seizures, muscle weakness, twitching, and hallucinations in a 6-year-old following propofol infusion. Propofol may have a dose-dependent anticonvulsant effect by enhancing GABA and inhibiting NMDA receptors but can sometimes trigger seizures and EEG changes due to GABA agonism and glycine antagonism, particularly during anaesthesia induction or emergence [20]. Emergence delirium (ED) affects 12–13% of children postoperatively, causing irritability and negative behavioural changes [20-22]. Ing and colleagues studied the Western Australia Pregnancy Raine cohort, examining 148 children exposed to general anaesthesia. At age 10, anaesthesia exposure longer than 35 minutes was linked to increased risks of language deficits. In another study of 38,493 children under 5, general anaesthesia exposure was linked to an increased risk of childhood mental disorders, with a hazard ratio of 1.26. Hu and colleagues studied 1036 children and found that those with multiple anaesthesia exposures before age 3 had worse academic performance and higher rates of learning disabilities (HR 2.17) and ADHD (HR 2.59) than unexposed children [21]. A study of 217 childhood leukaemia survivors treated with chemotherapy found neurocognitive impairments in 42% of patients, linked to cumulative anaesthetic duration, total propofol dose, and isoflurane exposure across multiple treatments [22].

Mitigation Strategies and Future Directions

Long duration, repeated exposure and use of multiple anaesthetic agents can increase neurotoxicity, and cognitive and behavioural functioning disorder [23]. Out of this concern, for clinical practice, if anaesthesia exposure is inevitable, it is essential to try to limit the duration and number of anaesthesia and the dose of anaesthetic agents. It is also feasible to consider alternative and mitigating treatments [24]. Since GA is an essential component of surgical techniques, it is challenging to evaluate its impact on people without reference to surgery. Of many known anesthetic agents, sevoflurane along with propofol is used widely in pediatric surgery [24]. There are currently many studies on the drug's role in developmental brain injury. Propofol's neurotoxicity is accompanied by a decrease in nerve cell func-

tional connectivity, which weakens signal transmission. Alternative agents can be used to prevent propofol-induced developmental brain neurotoxicity in children [25]. Xenon and Dexmedetomidine (DEX) are already used in clinical settings for neuroprotection and anaesthetic-sparing effects [23]. Dexmedetomidine, a central α 2 adrenoceptor agonist, is commonly used in the clinic for sedation, analgesia and anti-anxiety. Dexmedetomidine can attenuate propofol-induced apoptosis of hippocampal neurons and astrocytes and inhibit the proliferation of cells in the dentate gyrus.

Xenon is a rare inert gas with anaesthetic effects that can reduce neuronal damage. Some studies suggest, that if xenon and propofol were given concurrently, xenon prevented the decrease in neuronal differentiation that propofol-induced, lowered its damage to neural stem cells, and inhibited the differentiation of astrocytes. Numerous research has been conducted on preventative treatments against propofol neurotoxicity thus far, but their clinical efficacy and safety are still unclear. Further research is needed on propofol-protective measures [25]. However, children exposed to LA which is widely considered to be safe for neurological functions can be an ideal control group. Conversely, shorter and safer procedures like inguinal herniorrhaphy and ocular and dental surgeries usually done in LA have an overtly better neurological prognosis [24]. However, changes in the clinical management of children are not advised at this time. It is less important than the benefit of medical procedures for children [23].

Conclusion

Anaesthetic-induced neurotoxicity is a significant concern in pediatric anesthesiology. Animal studies and clinical trials suggest that frequency and duration of anaesthesia exposure contribute to neurotoxicity risk. Age-related vulnerability windows exist, with younger children (<3 years) exhibiting heightened susceptibility. Clinical trials (GAS, MASK, Sibling Study) show mixed results but suggest single exposures may not significantly impact long-term neurocognitive development. This research highlights the complex interplay between anaesthesia, neurodevelopment, and pediatric outcomes, emphasizing cautious clinical management and continued research.

Acknowledgements

Conflict of Interest

None.

Declaration

None.

Acknowledgments

None.

Funding

None.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.59.009248

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