Title

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Authors

Lee, Jean
Cisse, Farah
Flores, Crizel
et al.

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Jean Lee, Farah Cisse, Crizel Flores, Dan-Dan Guo, Rachael Lamden

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Abstract

General anesthesia (GA) is a widely used medical intervention, given to patients to eliminate pain during invasive procedures and surgeries, effectively revolutionizing the field of medicine. GA induces a reversible unconscious state by potentiating inhibitory receptors like GABA (γ-aminobutyric acid) receptors. Despite the practical uses of GA, recent studies have raised concerns about the potential risks associated with anesthesia exposure on the brain and cognitive function. In recent studies, these adverse effects, like neuronal death, can cause neurotoxicity despite the reversible and transitory nature of most GAs. In this paper, we discuss the neurological and behavioral outcomes after GA in developing and post-developed brains. These findings highlight serious concern on how GA impacts neurocognition and brain activity in both immature and mature brains and the potential harmful long term effects of GA. By understanding anesthetic-induced neurotoxicity, more avenues can be explored to particularly learn how to effectively protect vulnerable populations from harmful effects to the brain and warrant further research on clinical applications of anesthesia.

Introduction

Anesthesia is a crucial medical intervention widely used in clinical medicine to eliminate pain during a number of procedures including surgery, diagnostic tests, dental work and tissue sampling (Cleveland Clinic, 2020). Holding a pivotal place in the modern medicine landscape, anesthesia is an innovation that allows patients to drift off to “sleep” prior to any type of invasive procedure. In this reversibly induced unconsciousness, general anesthetics will be working to enhance inhibitory neurotransmission and reduce excitatory neurotransmission. By creating this anesthetic state, improvements in exposure and precision desired by surgeons can be made while

patients can undergo these procedures safely and comfortably. Anesthesia is provided by physician anesthesiologists who are licensed to administer anesthetics, which come in various forms and types, each with a distinct effect (Cleveland Clinic, 2020).

Types of Anesthesia

There are different types of anesthesia used for medical procedures, each with their own specific purpose. Local anesthesia is used to numb a small area of the body, and is commonly used for procedures like cataract surgery, dental work, or skin biopsies. Local anesthesia can be coupled with sedatives to relieve patient anxiety (Cleveland Clinic, 2020). Regional anesthesia is similar to local anesthesia but numbs a larger portion of a patient's body such as an entire limb. Like local anesthesia, patients can either be conscious or sedated depending on their pain and anxiety levels (Cleveland Clinic, 2020). Some forms of regional anesthetics include spinal anesthetic for hip or knee surgery and epidurals for labor, childbirth, or a cesarean section. General anesthesia (GA) requires the patient to be unconscious during the procedure and is usually given through an intravenous (IV) line or inhaled through a breathing mask (Cleveland Clinic, 2020). Patients go under GA in procedures that involve the head, chest, or abdomen.

Sedation is another option that makes the patient feel relaxed and drowsy. Patients are in a state where their awareness is depressed which limits their response to external stimuli. Through an IV, medications are given depending on the patient's pain level and type of procedure (Cleveland Clinic, 2020). There are different levels of sedation: light, moderate or deep. Compared to GA, sedation allows for normal involuntary organ function such as respiratory and cardiovascular functions (Cleveland Clinic, 2020). Some anesthesiologists prefer GA over sedation to have fully control and monitor these functions.

Biochemical Mechanisms of General Anesthesia

To understand the different effects of GA, it is important to understand the molecular mechanisms in the body that reveal their function. In the brain, cells communicate with one another with a variety of chemical messengers called neurotransmitters. During the process of chemical synaptic transmission, neurotransmitters diffuse across the synapse of two neurons and attach to specific receptor sites. Depending on a neurotransmitter's function, it can be classified as either excitatory or inhibitory. Excitatory neurotransmitters stimulate the target cell by depolarization to generate an action potential. Examples of such neurotransmitters are glutamate, acetylcholine, and histamine. Inhibitory neurotransmitters inhibit the target cell by causing hyperpolarization. By reducing neuronal excitability, it also decreases the chance of a neuron firing an action potential. Gamma-Aminobutyric Acid (GABA), an amino acid, functions as the body's main inhibitory neurotransmitter for the central nervous system (CNS) (Garcia et al., 2010). GAs enhances the activation of inhibitory neurons or reduces the activation of excitatory neurons. Consequently, receptors like GABA receptors are great targets of anesthetics (Garcia et al., 2010).

GABA receptors (GABARs) are divided into two subtypes: $GABA_A$ receptors ($GABA_A$Rs) and $GABA_B$ receptors ($GABA_B$Rs). $GABA_A$Rs are chloride permeable ligand-gated channels (Reynolds et al., 2003). They are mediated by the influx of chloride ions causing hyperpolarization of the membrane. This results in the mitigation of the excitability of neurons. $GABA_B$Rs are slower synaptic inhibitors than $GABA_A$Rs and are considered a G protein coupled receptor (GPCR) (Reynolds et al., 2003). Anesthetics usually amplifies the action of GABA-GABAR and in some cases several anesthetics in higher concentrations activate

$GABA_AR$s without the involvement of GABA. To increase the inhibition of these receptors, GAs allosterically regulate $GABA_AR$s which perturb the normal activation of GABA-ergic input (Garcia et al., 2010). Amnesia, a byproduct of many anesthetics, occurs even at lower concentrations of GAs. Even low concentrations of anesthetics like propofol and isoflurane can increase the GABAergic tonic currents in the hippocampus, the brain's memory and learning center (Reynolds et al., 2003). Although animal studies show an association between the mechanism of amnesia and GA, more research is needed.

Neurotoxicity

While many assume that GA is perfectly safe to use through surgical procedures, recent preclinical trials are starting to prove otherwise, especially in the safety of infants to young toddlers, and elderly patients. Analyzing these effects will improve our understanding of anesthetics and let us provide safer methods of utilizing this medication. Anesthesia has potentially harmful effects on the cognitive function of both children and adults. When young children are exposed to anesthesia during the developmental stages of their brains, they are at risk for neurodevelopmental disorders, lower academic achievement, and behavioral issues. On the other hand, adults are also at risk for similar issues. Some adults may experience difficult long-term adverse side effects such as memory loss and postoperative cognitive dysfunction.

GA has the potency to cause neurotoxicity which occurs when an individual is exposed to toxic substances which alter the chemical activities of the nervous system (INCHEM, 2001). Even alterations that are reversible like anesthesia are still regarded as damaging and can cause dysfunction. The duration of time under anesthetic drug exposure can increase the chance of neurotoxicity and could possibly alter the pathway of synaptogenesis (INCHEM, 2001). The

constant inhibition of nerve excitation with $GABA_AR$ antagonists is how many neurotoxicants function (INCHEM, 2001). This can lead to many symptoms, not exclusive to, dizziness, nausea, vomiting, and convulsions (INCHEM, 2001). Neurotoxicants can ultimately kill neurons and at worst cases lead to death. The risk of neurotoxicity is a concern for health workers as the use of anesthesia is necessary for certain invasive procedures.

Immature Brain

Animal Study

Neurotoxicity is a very prevalent concern when the immature brain undergoes anesthesia. Scientists have explored evidence of anesthetic toxicity in the central nervous system through an animal experiment (Perouansky, 2008). Specifically effects on an immature brain, excessive apoptosis can be the result of anesthetic use during the period of more intense synaptogenesis in the neonate. In the animal study of the immature brain, rat pups were anesthetized using a combination of midazolam, isoflurane, and nitrous oxide for 6 hours. They were then compared to a control group exposed to mock anesthesia for 6 hours through histopathological studies, behavioral studies in adulthood, and hippocampal plasticity. Upon recovery, the animals were split into three groups that were chosen at random. For histopathology research, the first group was utilized. The rats in the second group underwent a series of tests over a 160-day period as part of behavioral research on adult rats. The hippocampus plasticity in vitro (a model for learning and memory) was investigated in the third group. To assess overall health and development, the latter two groups were inspected and weighed every day. Isoflurane (0.75%–1.5%) produced a dose-dependent rise in apoptotic neurodegeneration, according to histopathology. The use of anesthetic drugs like isoflurane, midazolam, and nitrous oxide (N2O)

can cause damage to the brain cells of animals. Isoflurane caused a dose-dependent increase in cell death, while midazolam and N2O alone did not cause significant damage. However, when midazolam was followed by isoflurane and N2O, the damage was increased, especially in the thalamus and parietal cortex. This triple cocktail caused a 15-fold increase in apoptotic neurons and impaired learning and memory in rats. More research is needed to determine if these findings are applicable to humans.

Clinical Studies

In another study, differences in the risk of DD among young children exposed to GA are compared to unexposed individuals (Feng et al., 2020). This study includes a group of 989,753 patients with 34,371 children examined (11,457 children in the GA study group and 22,914 assigned to the non-GA control group). To examine the association between GA and developmental delay (DD), the patients were classified into three subgroups by frequency of anesthesia & three subgroups by total duration of anesthesia. DD-related ICD-9-CM codes were used to gauge neurocognitive outcome. The hazard ratios of developing DD following various amounts of anesthetic exposure were calculated using Cox regression models. The results suggest that children exposed to GA may be at higher risk of developing subsequent developmental disorders (Feng et al., 2020). Specifically, younger age at initial exposure to GA has been identified as a risk factor for developing DD, particularly in those exposed prior to 2 years of age. It has been hypothesized that GA may trigger apoptosis during neuronal development, which occurs more rapidly in early development. Additionally, this study found a higher hazard ratio of DD in boys compared to girls, and increased risks for DD in children with seizures, with hazard ratios ranging from 2.211 to 2.497 according to different levels of

anesthesia exposure (Feng et al., 2020). With more frequent anesthesia and longer overall anesthetic duration, this risk is further raised. Overall, these findings highlight the potential risks associated with GA exposure in young children and the need for further research in this area.

However, there is also research that denies how GA can cause developmental issues and instead evaluates magnesium's potential to prevent cerebral palsy in children at risk for preterm delivery was conducted (Robbins et al., 2021). GA in comparison to neuraxial anesthesia was the study exposure of interest. In the procedure, If a woman in the original research was at risk for giving birth prematurely before 32 weeks of pregnancy, she was randomly assigned to receive either prenatal magnesium sulfate or a placebo. Mothers who delivered a singleton, non-anomalous baby by cesarean section were included in this secondary study. If there were any gaps in the exposure or primary outcome data, those women were excluded. The main outcome was a composite score on the Bayley Scales of Infant Development II (BSIDII) at or above two years of age, corrected for preterm, indicating a mild, moderate, or severe motor or mental developmental delay. A BSIDII score of less than 55 suggests severe developmental delay, 55 to 69 indicates moderate delay, and 70 to 84 indicates mild delay. Assessments were done after two years. For categorical data, the chi-square and Fisher Exact tests, and for continuous variables, the Student's two independent samples t-test and Wilcoxon Rank Sum tests, differences were calculated. When the data distribution was skewed, Wilcoxon Rank Sum tests were applied. For the primary and secondary outcomes, multivariable logistic regression was used to account for potential confounding variables. Overall, 557 pregnant women from the original trial's 2241 randomly assigned participants are included in this analysis, and 119 (21.4%) of them underwent general anesthesia (Robbins et al., 2021). The key composite outcome of any developmental

delay according to BSIDII criteria was not increased by exposure to GA for cesarean birth. The general anesthetic group had a higher prevalence of motor delay (mild, moderate, or severe combined), but this difference did not hold in the adjusted analysis. GA was not linked to higher odds of light mental delay, moderate mental delay, severe mental delay, mild motor delay, or moderate motor delay in adjusted analyses of the BSIDII subdomains.

Mature Brain

Animal Study

In a recent study, scientists studied the effects of sevoflurane-induced neurotoxicity (SIN) on Sprague Dawley rats that were 13-18 months old (Xu et al., 2023). The first experiment separated the rats into the control and sevoflurane groups. The rats in the control group were left in a setting with pure oxygen for four hours while the sevoflurane group was left in a setting with 3% sevoflurane in 100% oxygen for an equal amount of time. In the next three experiments, the rats were injected with different types of anesthesia before they were put through the Morris water maze (MWM) test, elevated plus maze, and open field test, which all examined their memorization and learning capabilities. The rats that were exposed to the sevoflurane displayed abnormal behavior that mirrored anxious movements and cognitive dysfunction (Xu et al., 2023). Scientists later discovered through the use of RNA sequencing that the genes were downregulated after prolonged exposure to the anesthetic. Additionally, the number of synapses and dendritic spines was dramatically reduced, preventing both key learning and memory formation from taking place. Furthermore, prolonged exposure to anesthetics also increases neuroinflammation and alters the NF-κB inflammatory pathway, which triggers the expression of inflammatory genes (Xu et al., 2023). Overall, cognitive functions within adult rats can be

negatively impacted by prolonged exposure to anesthesia and produce anxious behaviors. These results may be applicable to humans as both organisms share physiological, genetic, and anatomical similarities.

Clinical Studies

Scientists found that mature/aged brains are more vulnerable to experience cognitive disturbances after exposure to anesthesia such as postoperative delirium and postoperative cognitive dysfunction. For instance, an adult has an up to 45% chance of being diagnosed with postoperative cognitive dysfunction (Wu et.al 2019). Moreover, 26% of elderly patients over the age of 60 years old are affected by cognitive disorders after being administered anesthetic for surgical procedures. Additionally, this study states that certain types of anesthesia are more effective and safer for aged patients compared to others such as propofol-based GA compared to sevoflurane. As the aged brain is more susceptible to harmful substances, a nationwide case-control noted that elders who undergo surgery and are administered GA are more prone to develop dementia-like symptoms. Furthermore, elderly patients may experience long-lasting cognitive impairments due to the neurotoxicity of the anesthesia (Wu et.al 2019). Overall, while the aging brain is not as susceptible to neurotoxicity induced by anesthesia as compared to the immature brain, the trauma-caused surgical procedures on an elderly person's body may lead to additional inflammatory responses, especially when exposed to GA.

However, a recent article disproves the notion that GA has a significant correlation with brain neurotoxicity (Reiger, Rondeau 2019). While numerous animal experiments have been conducted to assess the neurotoxic components of anesthetics, many of these studies have inferred that younger adolescents or animals are more likely to have neuronal apoptosis compared to mature adults. Moreover, though postoperative delirium and postoperative cognitive

disorder can occur after exposure to anesthetics, there are additional factors that result in cognitive dysfunction, as the direct biological pathway of their development is so far *unknown*. Effectively, other disturbances to human bodies such as an already present neural injury in the absence of anesthesia or ineffective methods of receiving and producing nutrients and oxygen can potentially cause decreased cerebral blood flow, leading to an increased risk of neurodegeneration in matured brains (Reiger, Rondeau 2019). Further, the article cites a meta-analysis of approximately seventy-five other studies, demonstrating that the correlation between the two cognitive disorders and any form of anesthesia was not significant. Specifically, the method of anesthetic administration had minimal effect on the cognitive dysfunction of matured brains. These findings suggest an inconclusive link between GA and the neurotoxicity of matured brains.

Discussion

The purpose of this literature review was to evaluate the correlation between general anesthesia and cognitive function. We extracted countless data from other clinical studies and animal experiments that included the risk rates of cognitive dysfunction in immature and mature brains. Within the articles we examined, we concluded that there is a significant correlation between the use of GA and an increased risk of cognitive impairments in individuals of all ages. However, one noticeable detail we found suggested that individuals within extreme age limits retained a higher risk of experiencing cognitive delays. More specifically, young children aged 1 year or younger and elderly aged 60 years or older have an increased risk of experiencing cognitive disorders due to either a less developed immune system or weakened immune system.

After analyzing an animal study and two clinical studies, it is found that there is a correlation between the use of GA in treatments and cognitive function in the immature brain. For instance, researchers concluded that using anesthetic drugs increased cell death and damage in multiple parts of the brain like the thalamus and parietal cortex (Perouansky, 2008). The increase of apoptotic neurons causes impaired learning and memory. The damage done can also vary depending on the order that the drugs are administered. These findings suggest that using anesthetic drugs on immature brains and infants should be carefully considered. It is crucial to be aware of the type of anesthetics used and the order in which they are injected in order to anticipate potential consequences that the drug may incur. Understanding these aspects of anesthetics can help professionals decide between administering the drugs or finding other alternatives that minimize the potential neurotoxicity that may come with anesthesia.

A clinical trial examined possible relations to younger children later having developmental delay because of the exposure to GA and being at higher risk of it triggering apoptosis in the neuronal development stage (Feng et al., 2020). These findings support how exposure in young children, specifically less than 1 year of age, may be associated with a higher risk of developing developmental disorders. These cognitive disorders can come in many forms such as learning disabilities Additionally, rather than an immediate effect, exposure to GA at an earlier age can cause effects later on in life, like poorer academic performance or difficulty in social interactions due to intellectual impairment. This further supports the idea that healthcare providers should carefully consider potential risks of general anesthesia exposure in young children and consider alternatives if necessary. Additionally, other factors such as gender should be considered when administering anesthetics as they indicate those who are at higher risk for developmental delays or seizures. However, there is research that denies this hypothesis. For

example, the outcomes of GA usage for cesarean delivery indicate that GA is not likely linked to mental delay in the children born after around two years of age (Robbins et al., 2021). This study highlights the different ways that GA can be administered to infants, which may be through the mother during birth.

As we assess the importance of finding a correlation between general anesthesia and cognitive ability, we also examine its effects on the mature brain. When humans mature from infancy to adulthood, their aging brains are more susceptible to cognitive decline and side effects from GA. More specifically, elderly patients are more vulnerable to medical conditions or are more likely to retain other injuries that require surgery. As such, their bodies are less likely to function at 100% capacity, depending on the environmental factors they face, which ranges from genetics to different types of lifestyle. Additionally, more than 40% of elders aged 60 years and older are likely to experience cognitive impairment in two different methods. The first method involves the difficulty of an elderly patient have to acquire new information. The second method involves their decline in memory retention, spatial cognition, and reasoning abilities. These two types of cognitive dysfunction are further exacerbated when they undergo surgeries and administered GA. In fact, GA targets certain parts of the central nervous system that are involved in cognitive abilities by preventing or slowing prefrontal choli generic neural activity. As a consequence, elderly patients are more likely to experience postoperative delirium or postoperative cognitive dysfunction. This vulnerability within an individual's body will leave it more susceptible to other inflammatory responses. Thus, understanding the impacts of GA on mature brains will enable healthcare workers to provide safer procedures in which GA is administered.

In addition to this, other animal experiments demonstrated that different types of GA lead to varied responses within the mature brain. For instance, scientists exposed a group of Sprague Dawley rats to multiple anesthetic agents to examine the depths of their reactions to neurotoxicity. The researchers found that sevoflurane based anesthetics have more significant results on cognitive function as compared to propofol based anesthesia. These results are reflected in another clinical study to which elderly patients demonstrated more vulnerability to postoperative complications after administered sevoflurane based GA. The scientists found that prolonged exposure to sevoflurane may downregulate certain genes involved with cognition and cause a reduction in synaptic plasticity and dendritic spines. As a consequence, elderly patients would experience a decline in memory retention and formation, leading them to an increased risk of developing dementia or other neurocognitive disorders. With all these factors considered, it is extremely important to evaluate the relative risks that come with using certain types of anesthesia. Moreover, these factors strongly indicate that additional research should be conducted to explore different methods that enable the reduction of these risks.

Limitations

When interpreting the results of animal and clinical studies investigating the effects of GA on both the mature and immature brain, it is crucial to acknowledge and carefully consider the limitations of each approach. The research in this field uses animal models widely, as opposed to human subjects. This design limits research on how the human system in specific is impacted, as the results of animal subjects may not accurately reflect on the human brain. In studies similar to the one mentioned before, the conclusions were drawn from the results of a study on rat pups to investigate the effects of GA on immature brains (Perouansky, 2008). However, it is important to note that these findings may not be entirely applicable to the human

brain as there are substantial differences in structure, development, and function between rat pups and humans. Moreover, the environmental conditions and experimental procedures used in animal studies may significantly differ from those used in human studies. For example, animals are often housed in confined laboratory settings that do not account for the complex environmental factors influencing disease progression or treatment response in humans. Therefore, while animal models remain a valuable tool in scientific research, it is important to approach their results with caution and to conduct comprehensive validation studies in human clinical trials. From the perspective of clinical studies and meta-analysis reviews, data collected are essential in understanding the effects of anesthesia exposure on the immature brain, but they also have limitations that should be considered when drawing conclusions. For instance, the retrospective nature of the study and the reliance on medical records to gather information could lead to inaccuracies and incomplete data (Feng et al., 2020). The study also failed to control for all potential confounding variables, such as genetics, environmental factors, and socio-economic status. Furthermore, the study only included data from a single country, which could limit the generalizability of the findings to other populations. Additionally, the study relied on a relatively short follow-up period, and long-term outcomes of children exposed to general anesthesia were not assessed. Likewise, another similar article lacked information on the effects of prolonged or repeated anesthetic exposures on neurodevelopment at all gestational ages (Robbins et al., 2021). The study's limitations highlight the challenges inherent in studying neurodevelopment and the need for researchers to consider and mitigate these limitations to ensure the validity and applicability of their findings.

Similar to the context of research on the immature brain, both animal and clinical studies exploring effects of GA on the mature brain are limited in their application. Researchers have

determined that sevoflurane based anesthetics are the most detrimental to the cognitive function of adult Sprague Dawley rats as compared to other anesthetics used; however, replicating these experiments in a human patient would violate numerous laws, leaving researchers in the dark as to how human systems are affected (Xu et al., 2023). Further, other genetic or environmental factors may affect the outcome of GA on the mature brain. According to the another recent study, elderly patients with prior medical conditions are more susceptible to the negative consequences associated with GA exposure (Reiger, Rondeau 2019). As each elderly patient comes with a different health history, the results from long term GA exposure would appear to be obscured. Moreover, as much of the data we collected on mature brains came from a meta-analysis, the evidence appears less credible than actual clinical studies. Overall, this experiment to determine the impacts of general anesthesia on the mature brain encounters a number of intertwined roadblocks

Future Directions and Research

While the literature offers relatively comprehensive research, there is more to be discovered and understood regarding GA on both the immature and mature brain. Integral to the future direction for the use of anesthetic drugs on the immature brain is an increasingly cautious and informed approach. The potential risks associated with exposure to GA in young children, particularly under the age of 1, are of serious concern and must be avidly considered on a case by case basis by healthcare providers and caregivers alike. With this, alternatives to general anesthesia for certain procedures in young children, such as regional anesthesia, are a viable approach and should be an option whenever possible. As a whole the literature regarding GA on the mature and immature lacks substantial longitudinal research. Long-term cognitive outcomes are not widely understood and this hole in the data prevents medical professionals from

accurately advising patients before undergoing surgery with GA. Longitudinal studies involving extended follow-up periods would be insightful, providing information on potential risk-factors, for instance, the development of neurocognitive disorders.

Although research has been done using brain imaging to look more closely at the brain's reaction to different forms of GA (Alkire et.al 1999), the results using this technique are not up to date and relatively inconclusive, thus more human neuroimaging studies would be advantageous in examining alterations in brain structure and functionality — this goes for both adults and children. Particularly within the realm of pediatrics, there is minimal research using neuroimaging techniques to examine the effects of GA on brain structure and functionality. In this vein, neuroimaging has the potential to be used more extensively, comparing the results of different anesthesia regimens. This includes variations in the type of GA used and duration the individual was put under, as well as the combined use of medications before and after the respective procedure. With this, it is of interest to researchers and medical professionals alike to understand how diverse anesthetic doses, agents and administration techniques impact the developing, as well as developed brain.

Strategies to mitigate cognitive risks is a related area urging more research. An example includes the prospective use of neuroprotective medications (Panahi et.al 2018), cognitive training programs (Hampshire, Sandrone, Hellyer 2019), or other up and coming interventions to counteract or interrupt possible negative effects of GA on the mature brain. Along with mitigation strategies, comes the importance of better assessing the role of genetic and pre-existing conditions, in addition to lifestyle patterns within patients prior to putting them under GA — identifying and comprehensively understanding these factors may allow physicians

to more accurately prescribe doses of GA, with a clearer idea of how it can affect the patient post-op.

Conclusion

This literature review demonstrates that exposure to GA in both the immature and mature brain can result in cognitive dysfunction. For instance, GA administration in the immature brain elicits a cognitive delay later on in life while the exposure to GA at an older age made these individuals more susceptible to neurocognitive dysfunction and anxiety-like behaviors. Conversely, there are certain limitations to this study which includes the restraints on animal experiments and a couple confounding results. Thus, the information presented in this study would be an important guide to the direction of future research on GA, in which alternative methods to anesthesia should be considered and different approaches to mitigate the effects of neurotoxicity could be examined.

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