

Effects of general anesthetics on the cognitive function of pediatric patients: A review

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Highlights

- General anesthetics may cause neurotoxicity.
- Single general anesthesia before 3 years of age does not affect cognitive function in pediatric patients.
- The effect of general anesthetics on the cognitive function of pediatric patients is related to the number of anesthesia sessions, duration and the depth of anesthetic exposure.

Abstract

The consequences induced by the use of general anesthetics and better options of the drugs in children and infants have been topics of controversy due to the concerns about their potential impact on cognitive function. To address these concerns and ensure the safety of pediatric general anesthesia, this paper reviews existing basic and clinical studies that have investigated the mechanisms of general anesthetics on pediatric cognitive function. In this paper, the basic research on neurotoxicity of general anesthetics and the clinical research on the effects of general anesthesia drugs on cognitive function in children in recent years were analyzed and summarized. Although some of the clinical studies have suggested that general anesthesia in children or infants may cause neurocognitive damage and a series of behavioral complications, the results of the retrospective studies need to be viewed with caution as they may lack effective control for relevant factors that could have impacts in the perioperative period. It remains uncertain whether general anesthetics affect the cognitive function of pediatric patients. Further research is needed to establish clear evidence-based recommendations for clinical prevention and treatment measures to minimize the potential risks associated with the use of general anesthetics.

Keywords: General anesthesia, pediatric patients, anesthetics, cognitive dysfunction

Introduction

Pediatric patients are more active, easily agitated and less cooperative during surgical procedures in a conscious state. As the development of anesthesia technology and the continuous updating of anesthetics, general anesthesia has become increasingly important in pediatric surgery. However, concerns have been raised regarding the safety of general anesthetics in children due to their immature brain and nerve development. Certainly, the factors causing pediatric cognitive impairment include not only the side effects of general anesthetics, but also

the influence of other drugs used in the surgery. Moreover, the adverse physiological state of the pediatric patients during the operation may also cause damage to their nerves, such as intraoperative ischemia, hypoxia, hypotension, acidosis, and stress reaction. This paper is devoted to summarizing the effects of general anesthesia drugs on the cognitive function of pediatrics. Studies have indicated that the effects of general anesthetics on the cognition of children may involve N-methyl-D-aspartate (NMDA) compensatory mechanisms, synaptic modification, β -amyloid ($A\beta$) deposition, and neurotrophic apoptosis [1]. Although several

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clinical studies have explored this issue, most of them are still in the early stages. Therefore, further research is needed to establish clear evidence-based recommendations for the prevention and treatment of the potential risks associated with the use of general anesthetics in children.

The primary references for this paper and the findings of each study are derived from authoritative textbooks, China National Knowledge Infrastructure and PubMed. To ascertain the definition of pediatrics, the growth and development of neuron and the physiological characteristics of children, we consulted textbooks such as Zhufutang Practical Pediatrics and Clinical Pediatrics. Additionally, to investigate the potential impact of general anesthetics on nervous system, we searched publications in China National Knowledge Infrastructure and PubMed, using keywords “neuro”, “anesthesia” and “pediatric”, and retrieved relevant articles published within the last five years. These articles were then sorted and analyzed according to their abstract and main text. Furthermore, to examine the relationship between general anesthesia and cognitive dysfunction of children, we also conducted a search using the keywords “pediatric”, “general anesthesia” and “cognitive dysfunction”, and then screened out the articles and sorted to obtain relevant clinical studies.

Definition of Pediatric

Generally, the neonatal period is the first 28 days after birth; infancy lasts from 28 days to one year after birth; early childhood is defined as the second and third years after birth; preschool lasts from 3 to 6 years of age; and school-age is from 6 or 7 to 11 or 12 years of age [2]. Most of the current studies on the effects of general anesthetics on pediatric cognitive function have focused on the early childhood period, and the reason is that the growth and development of the children before the toddler period is rapid, with a high incidence of anesthesia-related risk events, particularly in the neonatal and infantile periods [3]. So, the physiological characteristics of different periods should be taken into consideration for the safety management of anesthetics.

Neurophysiological characteristics of pediatrics

Pediatrics is a field of medicine that requires special attention due to the unique physiological characteristics of children. One of the most notable features of pediatrics before

early childhood is the rapid development of the central nervous system. During late pregnancy and the first few years postnatally, the brain develops rapidly, which is known as the period of explosive brain growth [4]. During this stage, nerve cells are differentiating, and synapses are being formed between neurons. Conditioned reflexes are also gradually being produced. However, the cortex is not yet mature enough to withstand hyperthermia, toxins, or other adverse stimuli. So, this period is particularly vulnerable to drugs that interfere with physiological functions. Numerous clinical studies have shown that many general anesthetics can cause morphological and functional changes in developing brain, including accelerating neuronal apoptosis. Large doses and prolonged exposures of anesthetics can significantly affect the nervous system, but it is hard to establish a definitive limit on the duration of general anesthesia which has no unequivocal effect on neurodevelopment [5]. Furthermore, the insufficient research and evidence on the long-term effects of general anesthetics also pose a significant safety challenge for general anesthesia in pediatric patients undergoing surgery.

Assessment of pediatric cognitive function

Cognition, the process of acquiring or applying knowledge and processing information, is considered to be the most fundamental aspect of human mental functioning. It encompasses a wide range of mental processes, including perception, sensation, memory, thinking, imagination, and language [6]. The main assessment methods commonly used clinically to test pediatric cognitive function include the Processing Speed Task, Wechsler Preschool and Primary School Intelligence Scale, 4th Edition, Working Memory Task, Mallen Fine Motor Scale, and the Purdue Nail Board [7]. The Processing Speed Task is a measure of basic cognitive functions that are essential for effectively processing information. The WPPSI-IV and Working Memory Task assess higher cognitive functions to predict children's cognitive abilities. The Mallen Fine Motor Scale and the Purdue Nail Board are tools used to assess learning abilities and behavioral problems [8].

Cognitive dysfunction is a disorder characterized by the impairment in one or more cognitive functions and would affect individual's daily life or social abilities [9]. When cognitive dysfunction is observed in children, it often manifests as specific disorders, including thinking disorders such as disorders of associative processes and logical thinking, memory disorders such as memory deficits and errors, and

perceptual disorders such as hypersensitivity or dulled sensations, as well as hallucinations [10]. These children may experience frequent mumbling, aphasia, and various psychiatric disorders. The impacts of cognitive dysfunction on children's lives are significant and can even be life-altering. Therefore, before conducting general anesthesia surgery on children, it is crucial to comprehensively assess the potential impact of anesthetics, surgery and other factors on their cognitive function. Safe and reasonable preparation for the operation should be carried out, with a focus on minimizing possible safety issues.

Common drugs used in pediatric general anesthesia

Intravenous anesthetics

Propofol

Propofol is one of the most widely used intravenous anesthetics in the world and is also the most commonly used anesthetics in pediatric general anesthesia [11]. Propofol has various pharmacological effects and properties, including anesthetic induction, sedation, analgesia, anti-inflammatory, antioxidant, immunomodulation, neuroprotection, antiplatelet, antiemetic, etc. [12]. Propofol mainly acts by activating the inhibitory amino acid receptor γ -aminobutyric acid (GABA) and inhibit the release of excitatory neurotransmitter to enhance GABA-mediated transmission. Its pharmacological mechanism is also associated with the regulation of GluN2B-containing N-methyl-D-aspartate (NMDA) and extracellular signal-regulated kinase 1 and 2 pathways in spinal dorsal horn neurons to exert analgesic effects.

Wang et al. reported that propofol could reduce the stress response during surgery, decrease the release of inflammatory factors, thereby alleviating neuroinflammation and protecting nervous system [13, 14]. Although most studies have concluded that propofol has neuroprotective effects, Yao et al. concluded that propofol might still cause postoperative cognitive dysfunction in pediatric patients, and this effect could be substantially eliminated in combination with sevoflurane [15, 16].

Etomidate

Etomidate is a commonly used short-acting intravenous anesthetic, which is commonly used clinically for the induction and maintenance of anesthesia for short surgical procedures, as well as pediatric general anesthesia [17, 18].

Etomidate has sedative, analgesic and intraocular pressure-lowering effects, and functions by regulating gamma-aminobutyric acid (GABAA) receptors, the main inhibitory neurotransmitter receptors in the mammalian brain, leading to a sedative-hypnotic effect.

However, Xu et al. reported that etomidate was neurotoxic, which may be related to its inhibition of excitation in developing neurons and the elevation of intracellular calcium ion concentration, leading to neuron damage and apoptosis [19]. At the same time, they also highlighted that etomidate had a strong inhibitory effect on developing neurons, which brought to light its potential impact on neurodevelopment in children. Yang et al. also noted through a comparative study that etomidate could lead to postoperative cognitive impairment in children [20].

Ketamine

Ketamine is the only intravenous anesthetic with a definite analgesic effect, widely used in clinical practice and general anesthesia in pediatric patients, with properties of anesthesia, analgesia, anti-inflammation and antidepressant [21]. It primarily targets on NMDA receptors, non-competitively blocking them and consequently producing analgesic effects [22]. It has been suggested that ketamine is an analgesic; meanwhile, it also agonizes opioid receptors and exerts analgesic effects.

However, it was suggested that ketamine may cause neurotoxicity and induce neuron apoptosis, and possibly lead to the abnormality of the phosphorylation of hippocampus-specific proteins, as well as the expression of neuronal cell receptors and the immunity of the nervous system [23, 24]. Su et al. suggested in their study that ketamine could cause cognitive deficits in pediatric patients, which may be closely related to its neurotoxic effects [25].

Inhalational anesthetics

Sevoflurane

Sevoflurane, as a widely used inhalational anesthetic, has different effects on the nervous system, circulatory system, respiratory system, liver and kidney functions [26]. Due to its high efficacy of anesthesia, it is used in the surgeries in all ages. Sevoflurane is particularly suitable for pediatric general anesthesia due to its characteristics of non-irritation, rapid induction and fast awakening [27]. It acts on the GABAA receptor [28].

Table 1. Receptors of commonly used anesthetics and possible effects on nerves

	GABAA	NMDA	AMPA	neurotoxicity
Propofol	++	-	-	yes
Etomidate	++	/	/	yes
Ketamine	+	-	/	yes
Sevoflurane	+	- [40]	- [41]	yes
Isoflurane	+	-	-	yes
Enflurane	/	-	-	maybe

Note: GABAA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; ++, significant excitation; +, excitation; -, significant inhibition; -, inhibition; /, no significant effect.

However, Liu et al. reported that sevoflurane increased neuron apoptosis and neuronal cell damage, impairing the plasticity of neural circuit [29]. In addition, sevoflurane has been shown to cause developmental neurotoxicity due to its τ phosphorylation and neuroendocrine effects [30]. Zhang et al. found that long-term anesthesia with sevoflurane in pediatric patients could cause damage to the hippocampus, which is likely to be one of the causes of pediatric cognitive dysfunction induced by sevoflurane [31].

Isoflurane

Isoflurane has similar pharmacological effects to sevoflurane, but has a pronounced effect of muscular relaxation. It is more effective in general anesthesia, so it is also widely used in surgeries [32]. Isoflurane primarily targets on multiple membrane proteins, including glycine and GABAA receptor, as well as the two-pore structure of the K^+ channel [33].

Many researchers suggest that isoflurane may be neurotoxic to developing brain [34]. This may be related to the fact that isoflurane is an NMDA receptor antagonist that can lead to neuron apoptosis [35]. Zhang et al. reported that isoflurane might cause damage to the cognitive function in pediatric patients, and this effect may be more serious than the adverse effects caused by sevoflurane [36]. Deng et al. found that exposed to isoflurane over 3 hours may cause higher positive rate in Denver Developmental Screening Test (DDST), suggesting a potential risk in the development of children [37].

Enflurane

Enflurane has moderate intensity, faster efficacy of induction and awakening, with a wide range of safety. It acts on NMDA receptors and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, which affects synaptic transmission.

Zhang et al. reported the neurotoxicity of enflurane and suggested that it may cause post-operative cognitive dysfunction [38]. Liu et al. revealed that this may be related to the significantly elevated levels of β -amyloid and phosphorylated tau in the hippocampus at an early stage [39]. The targets of various anesthetics and the possible toxicity are shown in **Table 1**.

Compound anesthesia

Most of the pediatric general anesthesia procedures are now performed using compound anesthesia, combining inhalational anesthesia with intravenous anesthesia, to achieve better effects. The most used inhalational anesthetic is sevoflurane, while the most used intravenous anesthetic is propofol, both of which have the advantages of fast onset of action, short awakening time, less effect on circulation and better anesthesia effect [42].

Compound anesthesia has many advantages and is widely used, but it also has to face the common adverse effects of intravenous and inhalational anesthetics. Its effects on the pediatric nervous system can no longer be inferred from one single drug, but the interactions between different drugs, which is more complex and unpredictable. So, it is more important to study the effects of compound anesthesia on the cognitive function of pediatric patients.

Basic research on the neurotoxicity of general anesthetics

Numerous basic studies have illustrated that the effects of general anesthetics on the cognition in children may involve different factors, including NMDA compensatory mechanisms, synaptic modification, $A\beta$ deposition, neurotrophic apoptosis and so on. Possible mechanisms of cognitive dysfunction caused by general anesthetics in children are summarized in **Figure 1**.

Effects of general anesthetics on synaptic function

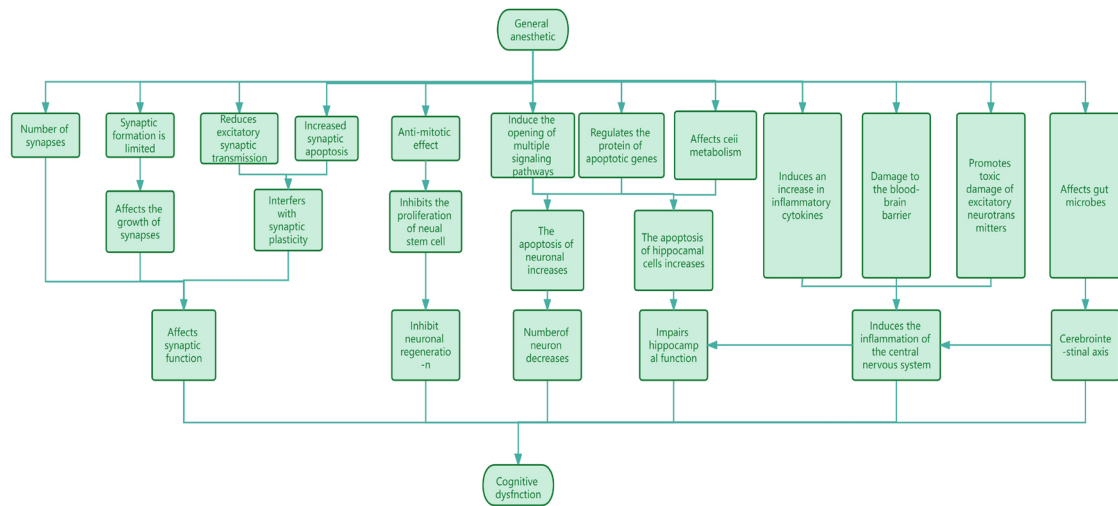


Figure 1. The possible mechanism of cognitive dysfunction caused by general anesthetics in children.

Synapses play a crucial role in learning and memory, serving as the foundation of long-term memory formation. The formation of synapses directly affects cognitive function which plays a major role in the development of pediatric neurological functions [43, 44]. Study has shown that sevoflurane induces spatial learning memory deficits in APP/PS1 mice, as well as elevates the production of intracellular A β , leading to the autophagy and impairment of synapses [45]. Moreover, study has indicated that general anesthesia can affect synaptogenesis in an age-dependent manner. Anesthetics may cause a decline in the number of dendritic spines and limited synapse formation during peak synaptic development [46]. In addition, anesthetics interfere with the normal physiological process of nerve regeneration and may regulate the growth of microglia, leading to postoperative cognitive dysfunction by mediating the decline in the expression of brain-derived neurotrophic factor (BDNF) [47, 48].

It was found that isoflurane could interfere with synaptic plasticity and lead to an increased apoptosis of synaptic spines [49]. Study also demonstrated that isoflurane reduced excitatory synaptic transmission in the hippocampus, affecting synaptic plasticity [50]. Shi et al. showed that isoflurane could cause changes in the presynaptic and postsynaptic membranes, as well as the destruction of synaptic vesicles [51]. These may be closely related to cognitive impairment.

It has been noted that ketamine abuse may decrease the expression of hippocampal postsynaptic density protein and affect the growth, plasticity, and transmission of excitatory synapses [23, 52]. These provide a possible direc-

tion for further investigation into how ketamine induces cognitive dysfunction.

Inhibition of neuron regeneration by general anesthetics

In the developing brain, neural progenitor cells have a greater capacity to divide and multiply, which also affects the development and maturation of the entire nervous system, especially the regeneration of neurons in the subventricular zone and the dentate gyrus of the brain, which play an important role in learning and memory [53]. Studies have found that general anesthetics, such as isoflurane, have inhibitory effects on the regeneration of neurons, which in turn affects the cognitive function in pediatric patients [54, 55]. The dose-dependent inhibitory effect of isoflurane on neural regeneration may be closely related to its anti-mitotic effect [56].

Yang et al. pointed out that isoflurane possibly inhibited the proliferation of the nervous system and made them prematurely differentiate into neurons, resulting in impaired cognitive function [57]. Gao et al. also showed that high concentrations of isoflurane inhibited the proliferation of neural stem cells in the dentate gyrus of the hippocampus of aged rats [21].

Similarly, Zhang et al. found that sevoflurane also affected the proliferation of neural stem cells by modulating RTN4, thereby leading to cognitive dysfunction [58]. Santos et al. noted that ketamine affected the proliferative regeneration of the central nervous system in zebrafish, but the effects on humans are unclear [59].

Effects of general anesthetics on the nervous system

Neuron apoptosis and the impairment of hippocampus function

Hippocampus, as a part of the limbic system, is mainly inseparable from the storage and conversion of short-term memory, as well as orientation and other functions. Therefore, hippocampus directly affect the learning and memory ability, as well as general cognitive function. Since general anesthetics can affect the normal physiological function of the hippocampus by impacting the apoptosis of neurons, they may also affect the cognitive function of pediatric patients. These anesthetics mainly activate GABAA receptors, inhibit NMDA receptors, and lead to sedative effect.

In 1999, Ikonomidou et al. found for the first time that after the administration of ketamine, a large number of apoptotic brain neurons were found in the brain of threats [60]. Subsequently, a large number of basic experimental studies on the cerebral neurotoxicity of general anesthetics emerged.

Liao et al. observed the hippocampal cells after exposing the rats in isoflurane and found that isoflurane triggered cell apoptosis by activating p38-MAPK signaling pathway [61]. Other studies have also shown that exposing to 3% sevoflurane for 4h caused increasing apoptosis of granule cells in hippocampus DG region, which was mediated by involving I κ B/NF- κ B /P65 signaling pathway, affecting the differentiation of late precursor cells in the dentate gyrus of the hippocampus to immature and mature neurons, and resulting in the recent spatial memory dysfunction in rats [62]. By establishing animal and cellular experiment models of isoflurane neurotoxicity, Yang et al. found that isoflurane could reduce mitochondrial membrane potential and promote the compensatory increase of respiratory chain function by opening mitochondrial ATP sensitivity potassium channels, and this process simultaneously contributed to the increasing production of reactive oxygen species (ROS), the excessive accumulation of which would disrupt energy production and activate the mitochondrial endogenous apoptotic pathway, resulting in cellular damage and neurotoxicity. These can lead to the impairment of cognitive function, specifically, learning and memory deficits [63].

Besides isoflurane, other anesthetics also have similar effects. Zhang et al. found that sevoflurane may cause excessive autophagy of hippocampal neural stem cells, in turn leading to cognitive impairment [64]. Su et al. revealed that

propofol could induce apoptosis and autophagy of hippocampal cells in mice [65]. High doses of propofol were also found to induce apoptosis in neurons, affecting the cognitive function of mice [66]. Ketamine was reported to increase the expression of cellular caspase-3, causing neuron apoptosis and affecting the cognitive function of young SD rats [67].

Generally, most of the animal research aimed to investigate how the anesthetics function on different signaling pathways, the production of proteins encoded by apoptotic genes and the cellular metabolism. These studies indicate that anesthetics could induce neuron apoptosis and the damage of hippocampal region, affecting the cognitive function of the animals. However, the precise mechanisms of hippocampus damage are still unclear [68].

Inflammatory responses in the central nervous system induced by anesthetics

The effects of general anesthetics on pediatric cognitive function are primarily attributed to their impact on the developing nerve cells, including affecting the number of neurons, promoting apoptosis, as well as affecting the inflammatory responses of nervous system, which induces the increase of inflammatory factors [46, 69]. Numerous studies have indicated that cognitive dysfunction is resulted from the reduction of the number of neural stem cells and formation of neurons, as well as developmental neuroinflammation [70].

Hu et al. found that isoflurane induced an increased expression of inflammatory factors such as IL-1, IL-6 and TNF- α in the brain of mice [71]. The accumulation of a large number of inflammatory factors damages hippocampal neurons are "important players" in the transmission of information in the central nervous system. The accumulation of a large number of inflammatory factors creates long-duration potentials that inhibit the function of hippocampal neurons, leading to the alterations of their function. This promotes the development of excitatory neurotransmitters, such as glutamine, thereby inducing the inflammatory responses in central nervous system [72]. These may cause reversible or irreversible damage to the cognitive function of children.

Huang et al. stated that possible mechanisms of sevoflurane-induced inflammatory responses in the nervous system include the modulation of microglia function, the disruption of the blood-brain barrier (BBB), the alteration of intestinal flora, and the alleviation of cholinergic

neurotransmission [73]. Hou et al. also pointed out that sevoflurane could induce IL-6 secretion and trigger the inflammatory response in the nervous system. Sevoflurane may also activate microglia, and the inflammatory responses triggered by sevoflurane can result in postoperative cognitive dysfunction [74-76].

Hou et al. found that propofol could target the activation of transglutaminase 2 (TGM2)-mediated or NF- κ B-mediated signaling pathways [77]. Guan et al. reported that propofol could down-regulate ROS/PI3K/Akt/mTOR/HIF-1 α signaling pathway activity, while Liu proposed propofol might mediate immunomodulatory mechanisms [78, 79]. These possible mechanisms could result in the suppression of microglia and attenuated inflammatory responses of the nervous system, which is also considered one of the reasons for the neuroprotective effects of propofol [80].

Effects of general anesthetics on gut microbiology

Gut microbiology has been a hot topic of research in recent years, and studies have found that anesthetics may influence gut microbiology, and the changes of intestinal flora caused by anesthetics may contribute to postoperative cognitive impairment [81, 82]. Lu et al. suggested that gut microbes may influence neurological function through the brain-gut axis, leading to cognitive deficits, but the role played by the brain-gut axis is not clear yet [83]. Similarly, others also found that anesthetics might cause changes in the composition of gut microbes and lead to inflammation [84]. Moreover, anesthetics can cause the impairment of the BBB, which can further induce neuroinflammation, leading to neurological damage and impaired cognitive function.

Clinical research on the effects of general anesthetics on the cognitive function in pediatrics

The study of neurotoxicity of anesthetics aims to investigate whether general anesthesia has an impact on neurological function and its potential mechanisms. However, the question of whether this effect causes cognitive dysfunction in pediatric patients still requires further assessment by clinical studies and evidence-based medicine. In recent years, numerous retrospective clinical studies have been conducted to explore the effects of general anesthesia on pediatric cognitive function.

Hu et al. conducted a retrospective study on

over 1,000 children, divided them into two groups based on whether exposed to general anesthesia before the age of 3, and assessed their cognitive functions via medical testing and school follow-up [71]. Their results revealed that changes in cognitive function induced by general anesthesia in children may be associated with the number of times they received general anesthesia before the age of 3, and a single exposure to general anesthesia medication was not associated with any abnormalities in cognitive function. Shi et al. conducted a retrospective study on 61 children and also showed that general anesthetics did not cause cognitive dysfunction in pediatric patients within 3 months after surgery [85].

Nevertheless, there are studies that suggest general anesthetics may have long-term effects on cognitive function in pediatric patients [86]. Partanen et al. proposed that prolonged exposure to general anesthetics was a risk factor for clinically significant neurocognitive decline [87]. Additionally, in preterm infants who underwent surgery for conditions such as congenital heart disease and necrotizing small intestinal colitis, researchers found that general anesthetics could also lead to cognitive dysfunction [88].

The majority of such retrospective clinical studies have concluded that a single general anesthetic procedure before the age of 3 will not result in long-term cognitive dysfunction [89]. However, multiple general anesthetic procedures before the age of 3 may cause cognitive dysfunction and even long-term effects on cognitive function in children [90]. This may be linked to the rapid development of the nervous system and brain in the neonatal and early childhood period [91].

Currently, larger-scale clinical prospective studies worldwide are the Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) study, the Mayo Children's Anesthesia Safety (MASK) study, and the General Anesthesia or General Anesthesia in the Waking Region (GAS) study. Compared to retrospective studies, these prospective studies are well-planned and have clearer research objectives. In contrast, retrospective studies have practicality and induction, and different conclusions can be drawn from these two types of studies with different reference values.

According to the summary data, the latest PANDA study conducted neuropsychological test between children aged 8-15 who had undergone hernia surgery and their siblings and obtained inconsistent neurodevelopmental assessment

Table 2. Summary of clinical studies in recent years

Title	Author	Year	Research subjects	Research	Possible mechanism	Findings
Association between Exposure of Young Children to Procedures Requiring General Anesthesia and Learning and Behavioural Outcomes in a Population-based Birth Cohort.	Hu D [71]	2017	Children under 3 years of age	A comparative study of cognitive function in children exposed and unexposed to general anesthesia before the age of 3 years to investigate whether there is an effect of general anesthesia on pediatric cognitive functioning.	Exposure to general anesthetic drugs leaves immaturely developed nerves vulnerable. Adverse effects due to surgical operations, such as surgical stress reactions.	General anesthesia causes cognitive changes in children that may be related to the number of general anesthetics received before the age of 3 years, and single exposure to general anesthesia drugs did not reveal abnormalities in their cognitive functioning.
Neuropsychological and Behavioural Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia: The Mayo Anesthesia Safety The Mayo Anesthesia Safety in Kids (MASK) Study	David O [7]	2018	Children under 3 years of age	Unexposed, individually exposed and multiply exposed children born in Olmsted County, Minnesota, from 1994 to 2007 were sampled using a propensity-guided approach and underwent neuropsychological testing at ages 8 to 12 or 15 to 20.	Multiple, but not single, exposures to anesthesia are associated with an increased risk of ADHD, learning disabilities and reduced performance on the group-managed competence and achievement assessments, which was possible associated with child and family factors.	Anesthesia exposure before age 3 years old was not associated with deficits in the primary outcome of general intelligence.
Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial A randomised, controlled equivalence trial	McCann ME [94]	2019	Infants with a gestational age of less than 60 weeks	Infants with a gestational age of less than 60 weeks, randomly receiving awake regional anaesthesia or sevoflurane-based general anaesthesia and undergoing inguinal hernia, who had no previous risk factors for general anaesthesia or neurological injury.	Both hippocampal and non-hippocampal memories are deficient. Potential for cumulative effects on subtle individual or multiple deficits in skills development.	Slightly less than 1 hour of general anaesthesia in early infancy does not alter neurodevelopmental outcomes at 5 years of age compared with awake regional anaesthesia.
Longitudinal associations between exposure to anaesthesia and neurocognitive functioning in pediatric medulloblastoma.	Par-tanen M [87]	2021	Children before and after the age of 3 years	Pediatric medulloblastoma patients receive risk-adapted craniospinal photon irradiation followed by four cycles of high-dose chemotherapy and stem cell salvage. Neurocognitive testing was completed at study baseline (post-surgery and <2 weeks after initiation of radiation therapy) and annually for 5 years.	Anesthesia may induce apoptosis and cell death, thereby affecting neurological and cognitive development. General anesthetic drugs may selectively target damage to the hippocampus and learning performance.	Increased anesthetic exposure is a risk factor for clinically significant neurocognitive decline, in addition to age at diagnosis and treatment risk group factors.
Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis.	Caleb lng [92]	2021	Children under 18 years of age	Studies evaluating neurodevelopmental outcomes and prospectively enrolling children exposed to a single GA procedure compared with unexposed, and outcomes were evaluated using random-effects meta-analyses.	Influence of subjective parental factors.	A single GA exposure was associated with statistically significant increases in parent reports of behavioral problems with no difference in general intelligence.
Longitudinal assessment of cognitive function in young children undergoing general anesthesia.	Shi Y [85]	2022	Children aged 2.5-6 years	A retrospective study of 61 children undergoing general anesthetic surgery	Neurodevelopment impairment caused by perioperative event take years to become apparent, and may be improved by surgery.	General anesthesia for elective surgery in young children is not associated with a decline in working memory, processing speed and fine motor skills in the first 3 months postoperatively.

Title	Author	Year	Research subjects	Research	Possible mechanism	Findings
Multiple General Anesthesia in Children: A Systematic Review of Its Effect on Neurodevelopment	Colletti G [95]	2023	Children under 4 years of age	Pooled analysis by summarizing the main literature and clinical studies of recent years.	Cognitive deficits induced by multiple exposures to general anesthesia may identify an increased risk of anesthesia-related neurotoxicity. Association between multiple general anesthetic procedures and deficits in certain neuropsychological skills.	Controlled studies on mGA administered before 4 years of age agree that there is a higher risk of neurodevelopmental delay in children receiving them.
Association Between Receipt of General Anesthesia During Childhood and Attention Deficit Hyperactive Disorder and Neurodevelopment	Song JY [97]	2023	Children with a median age of 3.75 years	Follow-up and research analysis of children under 3 years of age undergoing general anesthesia to find associations between general anesthesia and adverse neurodevelopmental and behavioral disorders in children.	Repeated and prolonged exposure to general anesthesia in children under 3 years of age may cause neuronal damage. General anesthesia during periods similar to infancy and early childhood alters prefrontal cortex and reduces axonal connectivity. Exposure to anesthetics may induce developmental neurotoxicity and accelerate neurodegeneration in young children.	Exposure to general anesthesia with ETI in children is associated with an increased risk of ADHD and adverse results of neurodevelopmental screening test.

Note: ADHD, attention deficit and hyperactivity disorder; ETI, endotracheal intubation.

results [92, 93]. The MASK study was a comparative study of 308 single-exposure general anesthesia children under 3, with 206 multiple-exposure children and 411 unexposed children selected from the same community [7]. Children under 6 months of age were divided into two groups, a general anesthesia group and a local anesthesia group for comparison [94]. These three studies arrived at very similar conclusions, indicating that there were no significant differences in cognitive function between single anesthesia-exposed and unexposed children [95]. Moreover, a clinical trial also found that single anesthesia may not cause neurodevelopmental effects [96]. However, a secondary analysis of the MASK study suggested that the number of anesthesia sessions was associated with the effects of anesthetics on cognitive function, and multiple sessions of general anesthesia in pediatric patients may result in the alterations of processing speed [97]. These may have neurodevelopmental effects. Although the differences were not significant, they were associated with a potentially increased incidence of impairments in internalizing behaviors and executive functioning.

This suggests that the three prospective studies align with the conclusions drawn from the retrospective studies. In summary, a single general anesthetic procedure administered before the age of 3 does not result in long-term cognitive impairment; however, multiple general anesthetic procedures administered before

the age of 3 may lead to cognitive impairment or even cause long-term effects on cognitive functioning in pediatric patients.

Meanwhile, Wang et al. conducted research on 76 children who underwent thyroglossal adenostomy and found that when the anesthetic depth index (Narcotrend anesthesia value, NT value) was between 80 and 94 under the monitoring of NT value, the removal of tracheal tubes could effectively reduce the risk of cognitive dysfunction in children [98]. This finding may offer new insights into clinical research, and it is consistent with previous studies that have demonstrated the influence of anesthesia duration on cognitive function [99].

However, the limitation of these studies might be that it is not possible to control all the potential influence factors such as the social, family, educational background of the children, as well as the psychological factors, which have great impact on their cognitive function. Additionally, due to the limitation of sample size, it is difficult to generalize the findings in most of the studies. Furthermore, it could be a great challenge to conduct psychological testing on large population, and subtle changes may not be detected in studies that involve the entire population. These limitations highlight the need to explore more appropriate solutions. The effects of general anesthetics on neurodevelopment and cognitive function in pediatric patients and the development of new anesthetics still require

a large number of rigorous clinical studies. A summary of relevant clinical studies in recent years is shown in **Table 2**.

Conclusion

Regarding the effects induced by general anesthesia on pediatric patients, most of the current research focus on whether general anesthetics influence the cognitive function and the possible mechanisms [100]. Scholars have also conducted studies and analyses on this issue, and a relatively unified conclusion was reached. Namely, general anesthetics may cause neurotoxicity by inducing neuronal apoptosis, inhibiting neuron regeneration, and impairing synaptic and autophagic functions [101]. Clinical studies generally agree that a single exposure to general anesthesia before the age of 3 years does not affect cognitive function, and that the effects of general anesthetics on cognitive function in children are related to the number of anesthesia sessions and the duration and depth of anesthetic exposure [102]. However, the specific mechanisms and effects on pediatrics cannot be fully determined at present, and further studies are needed.

In conclusion, most current basic and clinical studies have only been able to demonstrate that general anesthetics may have neurotoxicity, but the exact mechanism remains unclear. The effects of general anesthesia on cognitive function in children may be related to the number of exposures and the duration of anesthesia, but other factors such as surgical procedures and interferences cannot be excluded. Therefore, further research is needed to upgrade the experimental apparatus and improve the accuracy of assessment methods for the neurotoxicity of general anesthetics. It is necessary to conduct more prospective studies, coupled with retrospective studies, in the clinical aspect. There is currently no reliable basis to prove that general anesthesia has an effect on pediatric cognitive dysfunction, which requires future research to urgently refine the experimental protocol and clarify the precise impacts and mechanisms. These may be helpful to provide prevention measures and suggestions for anesthesia in children.

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