

Is Childhood General Anesthesia Exposure An Etiological Contributor to Cognitive Impairment?

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Funding: This work was supported in part by the National Natural Scientific Foundation of China (NSFC, 81660195).

DOI: <https://doi.org/10.15354/si.21.re005>

The authors declare no competing interest.

General anesthesia is necessary for patients to undergo surgery and invasive procedures. However, numerous preclinical studies have demonstrated widespread developmental neurotoxicity of the commonly used anesthetics and sedatives for the immature brain. Clinical studies also suggest a strong correlation between childhood anesthesia exposure and subsequent behavioral or cognitive impairment in adulthood. These findings have attracted increasing attention of anesthesiologists, pediatricians, and caregivers about the safety of anesthesia exposure in children, especially during early childhood. Herein, the aim of this review was to present the molecular mechanism of general anesthesia and its effects on the developing brain and introduce the recent clinical evidence of changes in cognition function post-childhood general anesthesia exposure. More importantly, some of the spots will be importantly discussed to scrutinize the phenomena; only in this way, it may help minimize or eliminate relevant risk factors.

Keywords: Anesthesia, General; Mental Disorders Diagnosed in Childhood; Cognition Disorders; Environment Exposure; Preventive Medicine

Science Insights, 2021 March 01; Vol. 36, No. 3, pp.251-259.

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WORLDWIDE, millions of young children undergo anesthesia every year (1). However, the anesthetic and sedative effect is considered to be transient and reverse quickly upon washout. However, in recent 15 years, mounting preclinical studies have demonstrated widespread neurotoxicity of commonly used anesthetics presented as structural and morphologic injury, functional impairments, and behavioral abnormalities in various species, including non-human primates. Whether similar effects also happen in the human brain attracts increasing attention of anesthesiologists, pediatri-

cians, and caregivers.

Commonly used anesthetics and sedatives regulate excitatory (glutamatergic) or inhibitory (γ -aminobutyric acid, GABAergic) synaptic transmission, neurotransmitter signaling (AMPA, acetylcholine, or serotonin), as well as ion channels expression (sodium, potassium, or calcium channels), all of which underlie neuronal activity and homeostasis. Thus, early exposure to anesthetics may induce long-term alterations in maturation and plasticity of the developing brain according to the biological mechanism.

However, the application of preclinical observations into clinical scenarios remains highly debated due to some underlying limitations. For example, animals are distinctive from humans in neuronal structure, neural developmental trajectory, and developmental age at exposure and usually overdosed relative to the human brain. Besides, enrolled animals are essentially healthy ones, without comorbidities, lack of surgical or painful stimulations, collectively rendering it challenging to extrapolate animal results to humans (2). On the other hand, although some human studies observe an association between childhood general anesthesia exposure and subsequent neurocognitive or behavioral deficits, others suggest the absence of such a link (3). Therefore, whether childhood general anesthesia exposure contributes or to what extent contributes to cognitive dysfunction is far clearly elucidated.

Given the uncertainties mentioned above, it is urgent to ascertain the potential adverse consequences of general anesthesia on young children. As early as 2009, the US Food and Drug Administration (FDA) has established a public-private partnership with the International Anesthesia Research Society (IARS) to appeal to Strategies for Mitigating Anesthesia Related Neurotoxicity Tots, or SmartTots (4). Then in 2012, the FDA, SmartTots, together with the American Academy of Pediatrics take the first step to release a consensus to convey an intense concern for childhood anesthesia exposure-related neurodevelopmental risk, recommend that elective surgery should be avoided in children younger than three years old, and importantly, warrant further large-scale clinical studies to elucidate the risk. Moreover, in 2016, the concern has heightened with FDA communique indicates repeated exposure or greater than three hours exposure to anesthetic and sedative drugs in children before three years old can harm the development of children's brains and suggests warning added to these drug labels (5). Thus, although several reviews have previously described this complex issue (6,7), it is still necessary to aggregate available pre-clinical mechanism studies and clinical studies results to further understand this phenomenon.

Molecular Mechanisms of General Anesthesia

Although the exact underlying mechanisms of general anesthetics are still not fully understood, in recent years, it is suggested that commonly used anesthetics act primarily via increasing inhibitory GABA receptor activity and/or blocking excitatory N-methyl-D-aspartic acid (NMDA) receptor activity (8). Most general anesthetics classes, such as propofol, etomidate, volatile anesthetics, and benzodiazepines, work by enhancing GABA receptor activity and GABA_A but not GABA_B receptor. GABA_A receptor antagonists reverse the anesthesia effects, indicating that the GABA_A receptor activation is a crucial anesthesia induction mechanism (9). Besides, certain general anesthetics classes, such as ketamine, act as NMDA receptor antagonists (10). Either knockout or blockade of NMDA receptors abates the anesthetic potency after exposure to nitrous oxide or ketamine (11). Moreover, recent reports have shown that voltage-gated channels and neurotransmitter transporters such as glutamate transporter type 3 can also be essential mechanisms for anesthesia induction (12).

General Anesthesia and Developing Brain

Mounting evidence in anesthetic neurotoxicity studies has suggested general anesthesia exposure during critical stages of neuronal network formation may induce developmental neurotoxicity, including structural and morphologic damage, functional impairments, as well as behavioral abnormalities in later life (13). In detail, structural or morphologic damage may be manifested as neuronal apoptosis, glial apoptosis, impaired plasticity of dendritic spines, and mitochondrial damage, endoplasmic reticulum stress, synapse formation, and stability impairment (14). Besides, functional impairments include impaired synaptic neurotransmission, the deficit in long-term potentiation, and faulty axon targeting. Herein, the possible underlying mechanisms will be discussed.

Most anesthetics act via GABA or NMDA receptors, mainly inhibitory and excitatory in the central nervous system. As an inhibitory receptor, GABA contrarily acts as an excitatory neurotransmitter in the immature brain. GABA_A receptor activation leads to Cl⁻ efflux and neuron depolarization. General anesthetics propofol and benzodiazepines can act via GABA_A activation, leading to excess neuron depolarization and neural excitotoxicity (15). Besides, as an NMDA receptor antagonist, ketamine exposure may significantly induce NR1 expression and neuronal apoptosis in perinatal rhesus monkeys (16). Further, NMDA receptors also participate in synapse development and maturation. NMDA antagonist MK-801 may trigger widespread neuron apoptosis in the developing rat brain, indicating NMDA receptor and Ca²⁺ homeostasis's essential role in neuronal survival for the developing brain (17).

Anesthetic exposure in developing neonatal could also lead to neurotoxicity via mitochondrial morphogenesis, integrity, and function impairment, resulting in an overproduction of reactive oxygen species (ROS). With the following nitrous oxide and isoflurane exposure, a clinical dose of midazolam may downregulate ROS scavenging enzyme superoxide dismutase at nearly 2-fold and increase ROS content by nearly 30% (18). Disturbed mitochondrial morphogenesis decreases the mitochondrial density, increases autophagy activity, and leads to long-lasting impairment in inhibitory synaptic neurotransmission. ROS scavenger, EUK-134, may effectively inhibit ROS production and prevent general anesthesia-induced cognitive impairment (19). Besides, imbalance of calcium homeostasis post-anesthesia is an ionic mechanism underlying neonatal anesthesia toxicity. Either NMDA receptor antagonism with MK-801 or GABA_A activation with isoflurane could disrupt Ca²⁺ homeostasis, leading to neuronal degeneration (20). Also, ketamine exposure increases glutamate release, further resulting in intracellular Ca²⁺ accumulation, forming a cascade to amplify the excitotoxicity mediated neuronal death (21).

Of note, other than neurons, general anesthesia also impairs oligodendrocytes and astrocytes. Astrocytes support immature neurons during development, provide structural support to mediate neuronal migration and axon growth, and release neurotrophins such as brain-derived neurotrophic factors that promote neuronal survival synaptic strengthening (22). Isoflurane could result in a 30% reduction in axonal growth in co-cultured glia and neurons (23); further, it also disrupts the cytoskeletal network of astrocytes, collectively resulting in neu-

rotoxicity for the developing brain (24).

Further, a combination of diverse anesthetics, which happens in clinical practice, shows long-term injury for the developing brain. When midazolam, propofol, and isoflurane administration to neonatal rats may induce prominent apoptosis throughout the brain, as well as hippocampal synaptic function deficits and persistent learning and memory impairments (25). In another study, the combination of midazolam, isoflurane, and nitrous oxide applied at the peak of synaptogenesis also induces significant neurodegeneration, possibly as a result of mitochondrial morphogenesis impairment and heightened autophagy activity (26). On the other hand, a wealth of preclinical studies shows the developing brain is most vulnerable to general anesthetics exposure; with higher concentration, longer duration, and repeated exposure during such rapid synaptogenesis period tend to induce more severe impairments (27).

Contraventional Evidence of Cognition Dysfunction from Childhood Exposure of General Anesthesia

General anesthetics act via modulating neuronal activity, and it is not implausible that such medication may intervene in the normal development of the human brain. Based on numerous preclinical studies, from rodents to non-human primates, it is well-accepted that general anesthesia is a contributory factor for cognitive dysfunction, including learning, memory, and social behavior (28). Meanwhile, the three latest extensive population-based clinical studies prove strong evidence of a slight increase in developmental risk (29-31). However, another two fails to prove a causal relationship between childhood brief anesthesia exposure and poor neurodevelopmental outcomes (32,33).

General Anesthesia: A Contributory Factor of Cognition Dysfunction

Most clinical studies are retrospective cohort studies, of which mixed and weak evidence is found for an association between childhood general anesthesia exposure and increased risk of subsequent adverse neurodevelopmental impairments (6). Further, the association is more substantial in those exposed to multiple exposures. If more detailed psychometric testing is used, deficits are presented in language, cognition, memory, and listening comprehension (34-36).

Recently, three extensive population-based studies have been published and provided strong evidence for a weak association between childhood anesthesia and some tests of school readiness (29-31). In O'Leary JD's study (29), the authors aim to explore the correlation between early childhood surgery and later performance in the early development index (EDI), a 104-component questionnaire encompassing five developmental domains. A total of 28,366 exposed children before EDI completion younger than 5-6 years old are matched to 55,910 unexposed ones, adjusting for aboriginal status, age, and household income. Those with a physical disability, health-related developmental impairment, and any behavioral or learning problem are excluded. Finally, the early developmental risk is slightly increased in the exposed (25.6%) compared with the unexposed group (25.0%), adjusted odds ratio, aOR 1.05 (95% CI, 1.01 to

1.08). In subgroup analysis, they also observed children aged 2-4 years at the time of exposure increased developmental risk compared with unexposed ones (OR 1.05; 95% CI 1.01 to 1.10). Whether or not there is no influence in the 0-2 years group cannot be validated until now.

Like O'Leary JD's study, Graham and colleagues also found strong evidence for a weak difference with exposed children doing slightly worse (30). Notably, they found single exposure during 2-4 years rather than 0-2 years was associated with deficits, most significant for communication/general knowledge (OR -0.7; 95% CI -0.93 to -0.47) and language/cognition performance (OR -0.34; 95% CI -0.52 to -0.16), while they found no evidence for a difference between single or multiple general anesthesia exposures. Another Swedish study compared 33,514 children experiencing one anesthesia exposure before four years of age with 159,619 matched controls (31). Similar to the previously mentioned two studies, they found strong evidence for a minimal difference. Single exposure before four years of age is associated with a mean difference of lower school grades (OR 0.41%, 95% CI 0.12 to 0.70%) and lower intelligence quotient (IQ) test scores (OR 0.97%, 95% CI 0.15 - 1.78%), and the impact is notably more significant in ear, nose and throat surgery.

However, the major disadvantage of a cohort study is poor control of confounding. For example, the two studies mentioned above' results may be affected by inclusion criteria confounding with the unidentified condition or brain injury enrolled that may influence neurocognitive function (29, 30). Further, these population cohort studies include only children undergoing surgery with general anesthesia, with children having simple invasive or diagnostic procedures requiring general anesthesia not explored. Thus, Francisco and colleagues conducted a large population-based record-linkage cohort study to observe developmental and school performance of children exposed to general anesthesia younger than four years old without preexisting neurodevelopmental disorders to exclude the influence of their distinct vulnerability for neurotoxicity (37). They found broad exposure had a 17%, 23%, and 34% increase of being high development risk (aOR 1.17; 95% CI 1.07-1.29), reading (aOR 1.23, 95% CI 1.12 - 1.36), and a lower score in numeracy below the national minimum standard (aOR 1.34, 95% CI 1.21-1.48), respectively. It remains associated with low numeracy after restricting to children with only one general anesthesia exposure and no other hospitalization. All of these studies collectively indicate general anesthesia exposure has detrimental neurodevelopmental outcomes in children.

General Anesthesia: A Noncontributory Factor of Cognition Dysfunction

Until now, General Anesthesia compared to Spinal anesthesia trial (GAS) is the only multicenter controlled randomized trial to compare the neurodevelopmental outcomes between sevoflurane-based general anesthesia and awake regional anesthesia (32). A total of 722 infants undergoing inguinal hernia repair are enrolled with median anesthesia duration of 54 min. The primary outcome is IQ scored at age 5, with results still unavailable. The secondary outcome is the composite cognitive score of Bayley-III, assessed at two years of age. Moreover, the

results showed that compared with awake regional anesthesia, just less than one hour of sevoflurane exposure in infancy did not increase the risk of adverse neurodevelopmental outcomes at two years of age (OR 0.17, 95% CI 2.30 to 2.64), providing strong evidence of equivalence between two groups about the four domains of the Bayley-III: motor, language, social-emotional and adaptive behavior. Subsequently, the research team continued to follow up on the above research objects for five years. It is suggested that just under an hour of general anesthesia in early infancy does not alter neurodevelopmental outcomes than awake-regional anesthesia in a predominantly male study population (3).

Another study, the United States multicenter Pediatric Anesthesia Neuro Development Assessment (PADNA), is by far the most robust cohort study yet to be published, and it proves strong evidence for no association between childhood anesthesia exposure and neurocognitive outcomes (33). In the PADNA, children aged 8-15 years with hernia repair before three years of age and matched siblings of similar age without hernia repair were enrolled. A detailed neuropsychological battery was assessed, with the global cognitive function being the primary outcome. Exposed children received inhaled anesthetics, and the median exposure duration was 80 minutes. And the results showed mean IQ differences between sibling pairs were as following: full scale (OR -0.2, 95% CI, -2.6 to 2.9); performance (OR 0.5, 95% CI, -2.7 to 3.7); and verbal (OR -0.5, 95% CI, -3.2 to 2.2). No significant differences were found between sibling pairs in neuropsychological outcomes, including memory, learning, motor speed, processing speed, visuospatial function, attention, executive function, language, or behavior. Further, subgroup analyses showed an up to 120min of exposure and exposure age did not affect the primary outcome. Of note, both GAS and PANDA are specific to a single indication and surgery type with relatively short general anesthesia exposure duration, making the results' generalizability limited.

The Focus of Debate

Timing of Childhood General Anesthesia

The vulnerability window is the specific neurodevelopmental stage when there is a maximal vulnerability to general anesthesia exposure (38). The same anesthesia exposure may cause substantial damage at the window of vulnerability, but a slighter one during other time points. Among species, an apparent heterogeneity of such window exists. Rodents appear to show a vulnerability window at postnatal day (PD) 7-10 (39,40). Simultaneously, non-human primates appear to be most vulnerable at PD 5-6, with humans at postnatal three years (41). Theoretically, it is plausible that neurotoxic phenotype post general anesthesia is positively associated with the age of exposure; however, not limited to the vulnerable window only shown by numerous studies.

It is still unclear the safe age of public exposure based on available clinical studies. However, numerous studies have observed neurotoxicity in children exposed from as young as < 6 months to as aged as ten years of age, specific medical conditions and surgeries among studies making it challenging to reach a consensus. Ing and his colleagues conducted a longitudinal cohort study to overcome such limitations, with a large popula-

tion of 38493 children before five years of age, and 192465 matched ones were enrolled (42). After exposure to anesthesia and single joint surgery, a mental disorder is evaluated, including developmental delay (DD) and attention deficit hyperactivity disorder (ADHD) in 11 separate age group such as exposure > birth admission to < 28 days, > 28 days, and < 6months, > 6 months and < 1 year, > 1 year and < 1.5 years. The study found children undergoing minor surgery requiring anesthesia before five years old have a small but statistically significant increase in DD (hazard ratio, HR 1.26, 95% CI 1.20-1.32) and ADHD (HR 1.31, 95% CI 1.25-1.37) at all age groups with the elevated risks not altered by the timing of the surgical procedure.

Such a slight but significant increase in the neurodevelopmental deficit is consistent with those mentioned above three sizeable population-based cohort studies (29-31). Of note, these three studies found an increased deficit in children exposed at older ages compared to those exposed at younger ages. On the contrary, an increased risk of language and cognitive deficit was identified in children younger than but not older than three years of age (43). These highly suggest that the vulnerable age tends to distribute evenly across the whole children's neurodevelopmental period; there might not be an upper age when anesthetic exposure and cognitive outcomes are no longer related. In another animal study, inhalational anesthetics exhibited conflicting neuroprotective and neurotoxic actions in adult mice and developing mice (44). Thus, the three-year-old suggested by the original FDA communique may be arbitrary, and postponing elective minor surgery to an older age might have little effect on the long-term neurodevelopmental risk.

Dosing of General Anesthesia Exposure

Dosing of general anesthesia exposure is another consideration of subsequent adverse neurodevelopmental outcomes. In Guerra's study, infants younger than six weeks with cardiac surgery are followed up at kindergarten age; multivariable linear regression was used to identify predictor variables of adverse neurodevelopment outcomes. The results found days on chloral hydrate was associated with lower performance in IQ (effect size -1.03; 95% CI -1.96 to -0.10; P = 0.03), and cumulative dose of benzodiazepines was associated with lower visual-motor integration score (effect size -0.07; 95% CI -0.12 to -0.01; P = 0.026) (45). Although the effect size for benzodiazepine exposure is so small to have limited clinical significance, this statistical significance should be taken cautiously, especially whether it predicts long-term impairment in academic and behavioral performance in adulthood is still unknown. A similar result was observed in another study to examine adverse neurodevelopmental outcomes in neonates experiencing complex cardiac surgery. After adjusting for various proved or suspected neurodevelopmental covariates, a larger volatile anesthesia exposure is associated with a lower Bayley-III cognitive composite score (P = 0.028), and a trend for lower language score (P = 0.056) examined at 12 months old, while a dose of fentanyl or benzodiazepines lacks such link (46). These studies indicate the cumulative dose of certain sedative or volatile anesthetic are potential contributors and serve as modifiable factors in the perioperative period.

Duration of General Anesthesia

Compared with hundreds of preclinical studies, few clinical studies available are designed to explore the exposure duration and adverse neurodevelopmental outcomes. Two previous clinical studies observed the effect of a specific duration of anesthesia exposure on learning disability and academic achievement, reporting an association between more prolonged anesthesia exposure and increased risk of neurodevelopmental disorders (47,48). Besides, Ing and colleagues applied a neuropsychological test, a more sensitive test to observe the relationship between the duration of volatile anesthetic exposure before three years of age and neurodevelopmental outcomes. Children were split into the following four exposure quartiles: ≤ 25 , > 25 to ≤ 35 , > 35 to ≤ 60 , and > 60 min, and they found compared with unexposed ones, children in the third and fourth quartiles that requiring >35 min of volatile anesthesia exposure had significantly lower performance in expressive language (49). At the same time, Wilder et al. identify duration of anesthesia exposure > 120 min as a potential toxic threshold (48). Moreover, the interim GAS study shows sevoflurane exposure with a mean duration of 54 min less than six months of age is not adequate to cause neurotoxic injury examined at two years old (32). Reasons for difference in duration discrepancy may result from the specific patient population or specific developmental test sensitivity. Besides, a more extended duration requirement for surgery sometimes indicates a more severe comorbid with a higher neurodevelopmental risk.

Further, Naumann and his colleagues show in children undergoing single suture craniosynostosis, every 30 min increase of anesthesia duration is associated with an estimated average decrease of 1.1 to 2.9 in developmental test score, a similar weak association is also observed with the increase of total inhaled anesthesia exposure duration (50). Other than anesthetic exposure, nonspecific effects of surgery or unmeasured confounding that closely related to surgery duration also contribute to such correlations. More evidence is warranted to elucidate the causal relationship between exposure duration and adverse neurodevelopmental outcomes.

Repetition of General Anesthesia A Single Anesthesia Exposure

Retrospective studies about whether a single anesthesia exposure could induce adverse sequelae in young children remain inconclusive. Some human studies find an association between single exposure and various adverse outcomes related to learning and behavior (29,30,35,47,51-53). For instance, Backeljauw B et al. found an association between only a single anesthesia exposure before four years of age and lower gray matter density in the occipital cortex and cerebellum measured at 5 to 18 years old, coupling with a decreased performance in intelligence and language comprehension (35). Similar functional magnetic resonance result and the adverse neuropsychological outcome was also observed by other retrospective studies (51,53). However, several studies observed no increased risk post a single anesthesia exposure during 3 to 4 years of age and subsequent academic performance, learning deficits, developmental abnormalities, or behavior disorders (47,54,55), similar results also observed in the recent randomized trial(29), and a sibling matched study with a more detailed neuropsychological assessment (33). It is

suggested that anesthetic effects on particular subdomains in one study may not be reflected in overall average performance assessed in other studies, combining the discrepancy in study design, collectively leading to the observed heterogeneity among studies.

Multiple Anesthesia Exposure

Although several extensive population-based studies find no evidence that multiple exposures impacted subsequent cognitive dysfunction (29,30), multiple anesthesia exposures are more ascertain to induce long detrimental effects on learning and behavior in some, but not all retrospective studies (29-31,48, 54-56). In a recent population-based birth cohort study, multiple but not single general exposures before three years of age are associated with increased frequency of ADHD and learning disabilities (HR 2.17, 95% CI 1.32 to 3.59). Multiple exposures are observed to induce impairments in both cognitive ability and academic achievements. However, a single general exposure, to a less extent, is only associated with a modest decrease in reading and language achievement but not cognitive ability (57). Of note, few studies explore the effect of children's exposure to general anesthesia via a relatively comprehensive neuropsychological assessment. Thus, the Mayo Anesthesia Safety in Kids (MASK) study adopted a detailed IQ standard score of the Wechsler Abbreviated Scale of Intelligence, as well as individual domains from a comprehensive neuropsychological evaluation and parent reports to observed neurodevelopmental outcomes in children experiencing general anesthesia before three years of age (58). This study shows either multiple or single exposures do not affect full-scale IQ.

Meanwhile, multiple exposures are associated with a decreased processing speed and fine motor ability and increased problems in executive function, behavior, and reading reported by parents. However, as in all observational studies, uncontrolled confounders such as health status and other neurodevelopment factors may affect outcomes. Further, procedural experience, including stress response to surgery and pain, may affect neurodevelopment, collectively rendering the definite causal relationship between multiple general anesthesia exposures and adverse neurodevelopmental outcomes far clearly determined through the above studies.

Interval of Multiple Anesthesia

It is not logical and unethical to perform a clinical study to observe multiple anesthetics' intervals on long-term neurodevelopmental outcomes in children, with available data primarily from preclinical studies. In Shen et al.'s study, rats exposed to sevoflurane exhibited a timing, dosing, duration, and frequency-dependent memory impairment observed in water plus maze, most importantly, repetition with a shorter interval (day 3 to 7) was more potent than that with a longer interval (day 3 to 14) in inducing impairment of adult memory (59). In a shorter interval, multiple anesthetics increased the total dosing and effective concentration (60), theoretically may cause more significant and more enduring effects. Of note, whether animal studies could translate to children needs further exploration.

Is Cognition Dysfunction the Definite Sequelae

of Childhood General Anesthesia?

Mounting preclinical studies have shown childhood general anesthesia exposure may induce timing, dosing, duration, and frequency-related neurotoxicity; however, whether or not such adverse outcomes are the definite sequelae of childhood general anesthesia is still inconclusive. Meanwhile, studies in human are also not able to sufficiently address this issue, in part due to reliance on various outcome measures such as group-administered achievement test, school record, individually administered test, or limited control for confounders such as surgery, concomitant comorbidity, socioeconomic status, and family environment, as well as the inability to verify exposure duration or specific anesthetic used. As thus, one recent editorial suggested that anesthesia associated neurotoxicity study will require longitudinal studies within a framework that includes analysis of pre-procedural factors of the child and anesthetic agent exposure, and contextual factors over the early and long term in order to tease out the potential effects of anesthesia in the context of the multitude of other factors that may affect child development (61). At present, most large population-based studies observed weak evidence between childhood anesthesia exposures and the following adverse academic performance or increased risk for behavioral disability, with risk more apparently only post multiple exposures. However, a single exposure to a minor surgery requiring brief anesthesia is observed to have no long-term neurodevelopmental risk. More high-quality human studies are warranted to further elucidate the exact impact of general anesthesia, especially in children experiencing prolonged or repeated neurodevelopment exposure.

Can the Threshold Points for General Anesthesia be set up in Childhood Exposure?

Before answering this question, many important fundamental questions remain to be answered: Are individual vulnerable pediatric patients at higher risk? Does anesthetic-associated neurotoxicity depend on specific timing, dosing, duration, or frequency of anesthetics exposure? Do concomitant comorbidities or inflammatory processes underlie the neurodevelopmental impairments? Even with these questions answered, exact threshold points are far clearly determined based on available studies. For example, although FDA warns that children younger than

three years old experiencing repeated or lengthy anesthesia exposure may suffer adverse neurodevelopmental outcomes. However, there is no solid rationale to support or deny using three years of age as a threshold. Further, most anesthesia exposure for children is within 2 hours, with sparse human data exploring exposure longer than 3 hours. Thus, although plentiful preclinical and clinical studies existed, the exact threshold values still need to be ascertained.

However, the detrimental neurodevelopmental outcomes primarily result from a synergy of excessive harmful stimuli in vulnerable stages, according to available preclinical and clinical studies.

What to do before Opening Pandora's Box?

Mounting studies in rodents and non-human primates have demonstrated developmental impairments, which directly lead to the FDA's warning on the use of anesthetics and sedatives during pregnancy and early life, significantly younger than three years old. However, the application of preclinical results into clinical scenarios remains highly debated due to some underlying limitations. Meanwhile, clinical studies in humans are still insufficient to demonstrate the adverse effects of anesthesia exposure on the developing human brain. There may be a weak risk associated with general anesthesia exposure. However, surgery without adequate anesthesia or analgesia is not an option. Thus, before opening Pandora's Box, it is more important to minimize or even eliminate such risk by reassuring new data from high-quality research.

Conclusions

General anesthesia is one of the most significant medical progresses, and millions of young children undergo general anesthesia every year to undergo surgery or invasive procedures. However, in the recent 15 years, a wealth of preclinical and clinical studies has indicated severe concerns regarding the effect of general anesthesia exposure on neurodevelopmental outcomes. As one public health issue, more additional high-quality research is urgently needed to understand the phenomenon better, improve understanding of its underlying mechanisms, and, importantly, devise mitigating strategies.

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Received: January 10, 2021 | Revised: January 20, 2021 | Accepted: January 26, 2021
