

MINI-REVIEW

Update on the effect of dental general anaesthesia on neurocognition in children

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Abstract

Dental general anaesthesia provides a comfortable treatment modality for children with early childhood caries and children's dental anxiety, but US Food and Drug Administration safety warnings have raised concerns about the neurotoxicity of general anaesthetic drugs. Currently, anaesthetic drugs have been found to impair neurocognitive function in animals, with possible mechanisms including cell damage, cell loss and impaired neuronal network function. The outcomes of clinical studies on the neurocognitive effects of surgical general anaesthesia in children have been inconsistent. However, studies focusing on dental general anaesthesia in children suggest that it does not affect neurocognitive function. In general, a growing number of studies suggest that dental general anaesthesia does not affect neurocognitive development in children. Moreover, dental general anaesthesia should be used as normal when other behavioural management is unavailable.

Keywords

General anaesthesia; Dental procedure; Neurocognition; Children

1. Introduction

Dental general anaesthesia (DGA) offers comfortable treatment conditions for children suffering from early childhood caries (ECC) and children's dental anxiety (CDA). DGA is a day-stay general anaesthesia procedure. The patient undergoes dental procedures in a state of unconsciousness induced by anaesthetic drugs, in which neither verbal nor painful stimuli can awaken the child; autonomic ventilation is impaired, and protective reflexes are partially or completely lost, necessitating airway management to ensure patient safety [1]. Since 1951, when Thomason first applied the technique of dental general anaesthesia, it has gradually become widely accepted due to its significant advantages. Dental general anaesthesia has been carried out internationally for 70 years and was first introduced into China in 1999. DGA is now established as a reliable treatment for children with ECC and CDA and has been actively promoted by domestic experts for the last decade.

However, the potential side effects of anaesthetic drugs in children, particularly infants, have been a major concern [2]. In view of the available research, the US Food and Drug Administration (FDA) issued a drug safety communication regarding general anaesthetic drugs in December 2016 [3]: relatively prolonged exposure to general anaesthetic drugs may have an effect on the neurodevelopment of children who have been exposed between the third trimester of pregnancy and the age of 3 years. In response to FDA warnings, more academics have taken a cautious approach. The American Society of Anesthesiologists (ASA) has argued that the cognitive and

behavioural effects of general anaesthetic drugs on children remain uncertain [4]. In a 2017 consensus statement, the European Society of Anaesthesiology and other medical societies suggest that there is currently insufficient compelling evidence to change current anaesthesia practice [5]. Therefore, the FDA added in the amendment to the drug safety communication on general anaesthesia that when it is necessary to use anaesthesia for patients, for example, in medical emergencies, the normal use of anaesthetic drugs should be adhered to [6].

Currently, controversy exists in the results on the neurocognitive effects of surgical general anaesthesia on children, among which there are still few studies on DGA. The aim of this paper is to review the studies on the neurocognitive effects of surgical general anaesthesia in children, especially studies focusing on DGA.

2. Preclinical data from animal models

A single prolonged exposure [7] or multiple short exposures [8, 9] to general anaesthetics have been found to cause significant neurocognitive developmental impairment in animal studies. Various types of general anaesthetic drugs can cause cognitive impairment in animals, affecting domains such as spontaneous activity, learning and memory function and mood. In recent years, a series of animal studies have been conducted under strictly controlled experimental conditions with the aim of clarifying the effects of general anaesthetic exposure on cognitive function and its biological mechanisms during development.

2.1 Cell damage

Cell damage caused by general anaesthetic exposure first occurs in the mitochondria and the rough endoplasmic reticulum during development.

General anaesthetic drugs can cause imbalances in mitochondrial fission and fusion and initiate a mitochondria-dependent apoptotic pathway [10], which ultimately affects how dendritic spines and synapses form, stabilize and function.

General anaesthetic drugs can modulate inositol triphosphate (IP3) receptors to induce intracytoplasmic calcium overload and ultimately lead to mitochondrial swelling and loss of control, as well as apoptosis and neuronal death in developing brain tissue [11, 12].

2.2 Cell loss

Various types of general anaesthetic drugs can lead to cell loss in brain tissue [13, 14], including neurons and oligodendrocytes. The main mechanism of cell loss is apoptosis. Exposure to sevoflurane led to neuronal and oligodendrocyte apoptosis in 7-day-old rhesus monkeys [15]. Cell-based experiments also suggest that autophagy may be involved in cell loss caused by exposure to general anaesthesia during development [16].

2.3 Impaired neuronal network function

Exposure to general anaesthetics alters the expression of synapse-associated proteins, resulting in impaired synaptic structure and function. In 7-day-old rats, the expression of synapse-associated proteins, such as synaptophysin, α -synuclein, N-cadherin, drebrin, synaptobrevin, amphiphysin, synaptosome associated protein 25 (SNAP-25) and Calcium-calmodulin (CaM)-dependent protein kinase II (CaMKII), decreases after exposure to propofol [17] and isoflurane [18] for 2–6 hours.

Exposure to general anaesthetic drugs affects synaptic transmission and plasticity. After 7-day-old rats were exposed to isoflurane for 6 hours, inhibitory synaptic transmission in thalamic reticular nucleus brain slices was reduced and excitatory synaptic transmission was enhanced by 14 days of age [19, 20]. Hippocampal long-term potentiation was diminished at 21 [21] and 30 [22] days of age.

3. Current state of studies on the neurocognitive effects of surgical general anaesthesia in children

The result of the Pediatric Anesthesia and NeuroDevelopment Assessment (PANDA) study [23] showed that 105 pairs of healthy children, who had a single exposure to anaesthesia prior to age 36 months, had no statistically significant differences in global cognitive function (IQ) scores at 8 and 15 years old compared to healthy siblings who had no exposure to anaesthesia. The scores did not differ significantly among different exposure ages (0–11 months, 12–23 months, and 24–36 months) or different exposure durations with 60-minute intervals (60 min, 120 min and 180 min). Meanwhile, in terms of domain-specific neurocognitive functions and behaviours,

such as memory/learning, motor/processing speed, visuospatial function, attention, executive function, language or behaviour, no statistically significant differences were observed. This study did not find an impact on children's neurocognitive development following a single short exposure.

The General Anesthesia and Awake-regional Anesthesia in Infancy (GAS) study recruited 722 infants for a randomized controlled trial, and the results published in 2016 [24] and 2019 [25] show that one hour or less of exposure to anaesthesia with sevoflurane does not result in neurodevelopmental abnormalities at 2 and 5 years of age, composite cognitive, language, motor, social-emotional scores or adaptive behaviours. This study did not find effects on children's neurocognitive development.

A study published in 2018 by the Mayo Anesthesia Safety in Kids (MASK) study [26] tested 997 children, and a comparison of unexposed, single-exposed, and multiple-exposed children before 3 years of age found no statistically significant differences in memory-related functions. However, there were significant differences in the neurological functions of learning and intelligence in multiply-exposed children; for example, there was a decrease in processing speed and fine motor abilities.

However, opinions differ. Smarttot, a multidisciplinary consortium of clinicians and researchers, reviewed the available preclinical and clinical evidence and concluded that exposure to general anaesthesia may have long-term effects on neurodevelopment in children based on current evidence. In addition, while deficits in cognitive function have not been demonstrated in children under three with exposures less than 3 hours, behavioural deficits have been noted following single, short exposures [27]. Charles *et al.* [28] conducted a meta-analysis of 31 studies and found that general anaesthesia in childhood had different effects on neurocognitive function in different periods. Danqing *et al.* [29] conducted a population-based birth cohort study and assessed the medical and school records of 1036 children (including 116 multiply exposed, 457 singly exposed and 463 unexposed) born in Olmsted County, MN, from 1996 to 2000. This study has shown that there is an association between multiple exposures and academic performance. Some researchers [30, 31] believe that the risk of adverse neurodevelopmental events is associated with anaesthesia exposure duration and frequency.

4. Studies on the neurocognitive effects of DGA on children (Table 1)

In 2021, 273 children (129 receiving general anaesthesia and 144 receiving local anaesthesia) underwent dental procedures under prolonged sevoflurane exposure (1–4 h) in China [32]. Assessment of neurocognitive function at 6 months postoperatively showed that DGA did not result in adverse neurocognitive outcomes or neurological deficits, and an evaluation of long-term effects should be conducted after 1, 2 and 5 years.

TABLE 1. Characteristics of studies on the neurocognitive effects of DGA on children [41–45].

Author	Year	Design	Data Source	Study Subjects			Exposure Duration	Procedure	Assessment Methods	Main Outcomes
				General Anaesthesia	Local Anaesthesia	Age at Exposure (yr)				
Pinping Zhou	2021	Prospective controlled equivalence study	Chongqing Medical University Dental Hospital	129	144	<7	110–160 min (median 130)	Dental examination, prophylaxis, fluoride treatment, fissure sealants, restorations, pulp therapy, stainless steel crowns, composite strip crowns, and extractions	WPPSI-IV (CN)	There were no adverse effects on neurocognitive function at 6 months postoperatively with sevoflurane-only anaesthesia in preschool children.
Xin Qi	2018	Prospective study	Air Force Military Medical University Dental Hospital	34	0	2–6	Mean ± SD time: (130.4 ± 21.43) min	Dental examination, prophylaxis, fluoride treatment, fissure sealants, restorations, pulp therapy, stainless steel crowns, composite strip crowns, and extractions	WPPSI-IV (CN), ABAS, BRIEF-P	The use of general anaesthesia once before 6 years of age has no significant effect on neurodevelopment at 6 months postoperatively.
Bin Xia	2016	Prospective study	Peking University Dental Hospital	28	0	4–6.5	Mean ± SD time: (163.4 ± 32.6) min	Dental examination, prophylaxis, fluoride treatment, fissure sealants, restorations, pulp therapy, stainless steel crowns, composite strip crowns, and extractions	C-WYCSI	DGA has no negative effect on the neurocognitive function of children exposed to general anaesthesia with sevoflurane, propofol and nitrous oxide for 2–4 h.
Keith Millar	2014	Prospective study	Glasgow Dental Hospital	58	0	5–14	Not specified	Extractions and restorations	Visual five-choice reaction time, maze drawing, coding, Rivermead Behavioural Memory Test for Children	The 24 h postoperative assessment showed that propofol and isoflurane similarly impaired reaction time, psychomotor coordination, and visual memory.
Keith Millar	2006	Prospective study	Glasgow Dental Hospital	48	48	5–10	Mean ± SD time: (11.13 ± 3.41) min	Extractions (2–16 teeth)	Visual five-choice reaction time, maze drawing, coding, Rivermead Behavioural Memory Test for Children	The 48 h postoperative assessment showed that the children’s choice reaction time and psychomotor coordination were negatively affected after short term sevoflurane-nitrous oxide anaesthesia.

WPPSI-IV (CN): Wechsler Preschool and Primary Scale of Intelligence-fourth edition (CN); ABAS: Adaptive Behavior Assessment System; BRIEF-P: Behavior Rating Inventory of Executive Function-Preschool Version; C-WYCSI: Chinese Wechsler Young Children Scale of Intelligence; SD: Standard Deviation.

In 2018, another domestic study [33] assessed the brain development of 34 children at 6 months postoperatively who underwent a single DGA and ultimately found no evidence of a significant effect of a single DGA on neurocognitive function in children aged 2–6 years, but further studies with larger sample sizes and longer follow-up are needed.

In 2016, Xia Bin *et al.* [34] demonstrated that there was no short-term decrease in Wechsler Intelligence Scale scores after 2–4 hours of DGA using sevoflurane, nitrous oxide and propofol by assessing the brain development of 28 children aged 4–6.5 years old at 2 weeks postoperatively.

In 2014, 58 children between the ages of 5 and 14 were randomly assigned to receive isoproterenol or isoflurane for DGA in England, and an assessment of reaction time (RT), verbal and visual memory, psychomotor coordination, and attention was performed preoperatively, immediately before discharge, and 24 hours after discharge (more than half of patients dropped out), showing that isoproterenol and isoflurane had similar adverse effects on reaction time, psychomotor coordination, and visual memory [35].

In another study in 2006, 48 children underwent tooth extraction under sevoflurane-nitrogen anaesthesia, and the other 48 children who received noninvasive examination without anaesthesia were used as controls. Cognitive assessment (visual five-choice reaction time, maze drawing, coding, Rivermead Behavioral Memory Test for Children) was performed prior to discharge and at 48 hours. The final results showed that some cognitive functions (visual five-choice reaction time, maze drawing) were affected [36].

In summary, the results from studies on the neurocognitive effects of DGA on children correlate with the duration of exposure to anaesthesia and the time of postoperative assessment. To prove this further, larger sample sizes and longer follow-up are needed.

5. Considerations in clinical studies of anaesthetic neurotoxicity

Since the initial observation by Morgan *et al.* [37] that the objective effects of general anaesthesia on neurocognition in children are unclear, numerous clinical studies have attempted to identify a link between general anaesthesia and prolonged neurocognitive deficits in children, especially after the 2016 FDA Drug Safety Communication. In the dental field, there is also an urgent need for evidence in support of the development of DGA. Currently, the results of studies on the neurocognitive effects of general anaesthesia in children are currently controversial, but the vast majority of DGA studies show no effect. However, the type of study design, sample size, the subjects' demographic information (*e.g.*, family income, parental education level), the comparability between the exposure and control groups, medical history, characteristics of surgery and anaesthetic drugs (frequency, duration, and type of surgery and drugs), age at exposure to general anaesthesia, frequency of follow-up, attrition, and outcome measures have made it difficult to synthesize and replicate the findings and to draw firm conclusions.

5.1 Anaesthesia-related factors

In basic research, factors such as the dose of anaesthetic drugs and the exposure duration in animal models fail to compare with common clinical conditions. To study the toxicity of general anaesthetics, animal studies have often involved repeated, high-dose, prolonged drug exposures far in excess of clinical requirements [33]. Anaesthetic requirements are much higher in small animals than in humans, with ketamine at 10 times the amount and propofol at 100 times the amount [38]. In some studies, low doses of ketamine, more similar to what paediatric procedures use, did not cause nerve cell death [39].

In clinical research, it appears that a single short anaesthesia session has no effect on neurocognitive development [23–26], whereas neurocognitive performance has been found to vary among children with multiple long-term exposures [26, 40]. The study by Pia *et al.* [41] showed that the neurocognitive effects of different anaesthetic drugs differ. The study by Wilder *et al.* [42] found effects of multiple anaesthetic exposures on neurodevelopment. In addition, the wide time span of patients and the fact that clinical anaesthetic techniques and medications have changed considerably may also lead to different results.

The newly published expert consensus by the Chinese Stomatological Association states that the duration of DGA should, in principle, not exceed 2 hours [2]. In addition, unlike most surgical general anaesthesia, intraoperative bleeding is rare, blood pressure control is not needed, muscle relaxation requirements are not high, and deep anaesthesia is not needed, so the anaesthesia delivery regimen is relatively simple, and short-acting anaesthetics are mostly used for inhalation or intravenous administration [34]. For this reason, researchers involved in the dental field believe that DGA is unlikely to have effects on children's neurocognition.

5.2 Systemic diseases and types of surgery

In the available studies, the underlying condition, surgery procedure and baseline data of the study participants were not completely consistent, so the effect of factors such as surgical stimulation on cognitive development could not be completely excluded [33]. According to previous retrospective studies, it is difficult to assess the independent effects of anaesthetic exposure because of disease and surgery co-occurring, such as cardiac and neurosurgical conditions that may be associated with neurodevelopmental abnormalities [43]. Adults may experience similar neurocognitive dysfunction as a result of stress associated with hospitalization, especially intensive care [5].

The DGA technique itself differs from most surgical general anaesthesia in several ways. First, the patients are in ASA Class I or II and in good physical health. Meanwhile, with the exception of handicapped children, most are free of systemic diseases or trauma that could affect their intelligence. Second, dental treatment is minimally invasive, and postoperative recovery is rapid. Instead of a hospital stay, the planned treatment is completed in a day clinic [2, 34]. Therefore, if you are wondering whether general anaesthetic drugs can affect the patients' intelligence, studies of DGA are better answer this important question than those of surgical treatment.

5.3 Assessment methods and timing

In regard to measuring preschool and school-age children's intelligence, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children-Revised (WISC-R), Raven's Progressive Matrices and Denver Developmental Screening Tests (DDST) are mainly used internationally, while the two revised Wechsler Intelligence Scales, Paediatric Examination Table of Neuropsychological Development under six (Paediatric Neuropsychological Table for short) and Developmental Screening Test for Child under six (DST) are mainly used in China. Currently, there is no unified and absolutely objective evaluation system. Different evaluation indicators have different emphases. Of the DGA literature included in this review, two used the WPPSI-CN, one used the C-WPPSI, and two measured items such as visual five-choice reaction time, maze drawing, coding, and the Rivermead Behavioral Memory Test for Children.

In the same study, the conclusions also differed slightly when using different assessment tools. In the PANDA study, no significant differences were found between the young children in the group with general anaesthesia and those in the control group on the primary indicator, the Wechsler Intelligence Scale, but on the secondary indicator, the parent-completed Child Behaviour Checklist (CBCL) completed by the parents, there were differences between the two groups of children [23].

In addition, the assessment duration varied according to the type of study (24 hours, 48 hours, 2 weeks, 6 months, 2 years, 5 years, *etc.*). The DGA literature indicating that general anaesthesia has an effect on children's neurocognition included in this review was assessed at 24 and 48 h postoperatively, whereas the metabolism and elimination of anaesthetic drugs also take time, and the reliability of this short-term measurement is questionable.

This also explains why current clinical studies show varying results. The development of a standard, rational and uniform assessment method is therefore a pressing issue.

5.4 Complexity of human neurodevelopment

In general, animal studies with good subject homogeneity and strict control of experimental conditions provide relatively reliable results. However, the generalization of results to humans remains controversial. The reasons for this are as follows:

First, compared to animals, there is a great deal of complexity in the structure and development of the human brain. It takes longer for nerve cells to mature in the human body than in other mammals. In rodents, the formation of key synapses and the refinement of their functions take only a few days or weeks, but in humans, it often takes months or even years [38]. Does this mean that humans have a longer window period of vulnerability, so that fewer nerve cells or synapses are vulnerable at any given time, reducing the potential for neural damage (if it exists)? Therefore, further studies will be necessary to verify whether the results in animal models can be extrapolated to humans.

Second, an animal experiment is different from a real clinical procedure, and the translation of animal data into clinical

evidence is fraught with uncertainty [44].

Therefore, more high-quality studies, such as multicenter, prospective cohort studies, should be carried out to provide more evidence.

5.5 Other factors

Other perioperative factors have been identified that may alter postoperative cognition and behavior [5]. In addition, various studies have found that genetic background, educational status, parents' financial situation and mothers' education may affect the credibility of the results.

6. Change in children's oral health-related quality of life following dental rehabilitation under general anaesthesia

Oral health-related quality of life (OHRQoL) is a comprehensive assessment that reflects the impact of oral diseases and their prevention and treatment on patients' physical, psychological and social functioning. Studies conducted in different countries with different questionnaires [45, 46] have confirmed the broad impact of ECC on children's quality of life. This not only causes pain and other discomfort but also affects the child's chewing, speech, aesthetics and other functions. Ultimately, it will affect the child's quality of life. To be worse, the teeth affect the child's ability to smile or speak and even seriously affect the child's overall physical and mental health. After the treatment, the child's symptoms, function, psychology and social interaction were greatly improved in all aspects. Not only is pain reduced and dental anxiety eased but also the function of chewing and aesthetics are restored and the quality of life is improved. In addition, the child no longer has to take time off from work to go to the doctor for dental problems. Meanwhile, in terms of the impact on the family, it reduces the need for parents to accompany their children to the clinic many times, which reduces and alleviates the parents' psychological and financial burden and improves the family's quality of life.

7. Conclusion

In conclusion, a review of the literature shows that a growing number of studies suggest that DGA does not affect neurocognitive development in children. However, neurodevelopment in children is the result of the interaction of multiple risk and protective factors, and it remains a challenging task in medical research to further explore the possible effects and mechanisms of general anaesthesia on the developing brain. For the provision of reliable evidence and the facilitation of synthesis and replication of studies, the effects of DGA on neurocognition in children require large-scale and well-designed cohort studies, including consistency in anaesthesia exposure and study design, tight control of confounding factors, and rigorous follow-up.

Therefore, taking into account the results of the current study, as well as the concerns of parents, we do see eye to eye with the FDA and recommend that for children with ECC

and CDA, outpatient treatment should be taken unless they are uncooperative, and the normal use of DGA should be adhered to when other behavioural management is unavailable.

ABBREVIATIONS

ABAS, Adaptive Behavior Assessment System; BRIEF-P, Behavior Rating Inventory of Executive Function-Preschool Version; CDA, child dental anxiety; C-WYCSI, Chinese Wechsler Young Children Scale of Intelligence; SD, Standard Deviation; DGA, dental general anaesthesia; ECC, early childhood caries; OHRQoL, oral health-related quality of life; WPPSI-IV (CN), Wechsler Preschool and Primary Scale of Intelligence-fourth edition (CN).

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

ZHC, MML, HCX and KC—had the idea for the article. ZHC—performed the literature search and data analysis and drafted the work. MML, HCX and KC—critically revised the work. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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