

Learning disorders related to exposure to general anesthetic in children

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Abstract

Background: There are many animal studies demonstrating increased neuroapoptose in the first periods of development, especially in stronger neural development regions. In young cobais neuroapoptose also noted, however, more localized area as the dentate nucleus and the olfactory bulb of the brain regions that show sinaptogênese even in adulthood and is responsible for learning.

Objective: To describe the current studies about learning disabilities and cognitive impairment related to exposure to general anesthetics in children.

Method: This is a systematic review, performed from the search in the PubMed database using the keywords "general anesthetics," "neurotoxicity", "children", "young child" and "pediatric" with the criterion inclusion, published in the last five years, in English and related exposure to anesthetics in human children . Were excluded from the articles concerning the studies in experimental animals or that they focus on side effects of other substances on the central nervous system, such as alcohol.

Results: So were found 108 articles. All were analyzed by two researchers individually. Only 27 met the inclusion criteria.

Discussion: In recent years, several studies have been conducted addressing neurotoxicity triggered by general anesthetics. The vast majority using experimental animals or stem cells. Suggest that both inhaled anesthetics such as venous are able to trigger the activation neuroapoptose with release of caspase 3:09, especially in phases of high growth and neural development. There is a strong association

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between duration of anesthesia and multiple exposures with learning disabilities and behavior.

Conclusion: Currently, you can not say that the damage caused by agents in animals can be replicated humans. However, the severity of outcomes, the FDA recommends avoiding anesthesia and surgery in children under three years, at least those that do not have an emergency basis.

Keywords: Neurotoxicity; general anesthetics; neuroapoptose; learning disabilities; children.

Introduction

Nowadays, anesthesia is performed everywhere in the world and its development has enabled the surgical approach of patients with increasingly severe conditions. The number of surgeries is growing every day and many questions have emerged regarding the safety of surgical anesthesia, especially in the age extremes (infants and elder). Several studies suggesting the neuroprotective effect of anesthetics and others suggesting neurotoxic effect have been conducted and the controversies only increase [1].

Nearly two centuries after the first report of ether use as an anesthetic, the general anesthetic's mechanisms of action are not fully understood. It is known that they act by binding GABA_A and NMDA receptors in certain brain regions. The connection to α 2-agonist receptors in the locus coeruleus (LC) also causes sedation, however without reaching a deep level of hypnosis. However, the mechanisms by which neural networks operate to produce the anesthetic state are still unknown. [2]

What is certain is that some anesthetics act by stimulating the inhibitory GABA receptor while oth-

ers inhibit the excitatory NMDA receptors and when the drugs act along the locus coeruleus their effect is potentiated, but they are unable to produce anesthesia alone. [2]

The halogenated have a more recent origin. The halothane had its clinical use released in 1956 and the isoflurane in 1981. They were all released very recently and the same way that we do not fully understand the mechanism of action of these drugs, we also do not know their long-term deleterious effects. [3]

It was revealed that general anesthesia would be a reversible state of unconsciousness and insensitivity induction that made possible the performance of surgical or diagnostic procedures and at the end the exposed individuals return to their initial state without any physiological or structural deficit.

Studies in laboratory animals suggest the possibility of deficits beyond the intraoperative. Especially in both of the age extremes, the exposure to general anesthetic may induce neuroapoptosis in specific brain regions, especially in neurons that are under development and accelerated synaptogenesis. These results, however, cannot be transposed to humans. [4]

However, several clinical trials are underway to try to clarify this question, and some are nearing completion.

Animal studies, using short periods of exposure to inhaled anesthetics in subclinical doses and followed by induced ischemia, has suggested neuroprotective effect of these drugs. However, more recent studies with therapeutic doses of inhaled anesthetics and for longer periods, has shown neurotoxicity. [5]

The studies that defend the ischemic preconditioning of inhaled anesthetics suggest their action decrease the metabolic rate of the brain, reducing the consumption of oxygen and probably increasing the release of nitric oxide. Those supporting the neurotoxicity, claim that there is an increase of neuroapoptosis triggered by the increased production of caspases, in addition to structural damage of neural cell in the cytoskeleton. Even studies in experimental animals are controversial. [4-8]

This question goes beyond, coming to the suggestion or not of the use of inhaled anesthetics in subtherapeutic doses for organ donors with brain death. Some defend the use of inhaled anesthetic, particularly isoflurane, suggesting its protective effect on ischemic preconditioning of the selected organs. [5,6]

Thus, the question is: Can general anesthetics in children lead to learning disorders? Thus, the objective was to describe the current studies about learning disabilities and cognitive dysfunction related to exposure to general anesthetic in children.

Method

This is a systematic review, performed from search in PubMed database using the keywords "general anesthetics," "neurotoxicity", "children", "young child" and "pediatric", it has as inclusion criteria , articles from the last five years; original articles with full access or only summaries; articles

with the keywords in the title; in english, review articles and studies in humans.

The exclusion criteria eliminated studies performed in experimental animals, stem cells or the ones that focused on side effects of other substances on the central nervous system, such as alcohol or drugs; as well as studies involving different anesthetic techniques of general anesthesia and studies that were in languages other than English.

Results

Initially, the search resulted in 108 articles, of which 27 met our search criteria. 81 were excluded and the reasons were: 34 repeated references, 6 regional anesthesia, 30 other subjects, 5 stem cells, 5 animal studies, 1 case report (**Figure 1**).

Table 1 summarizes the most important aspects of each selected article, the main author and a brief description of the sample.

Discussion

Among the articles found, only one corresponded to a retrospective cohort and another to a clinical trial. All the rest were review articles. Two large clinical studies are in progress, but they still have no conclusive results, the PANDA *study* and the GAS *study*. The latter is expected to be finished in 2015. However, they are aimed at assessing the vulnerability to general anesthetics in healthy children, ASA I and II, and their results cannot be extrapolated to children with comorbidities. [7,11]

It is interesting to observe that there is no significant amount of new clinical studies. However there are many review articles, reinforcing the concern that the topic brings up and the difficulty of preparing drawings that bring significant results, besides the ethical issues involved. The results of cohort studies are limited in their clinical applicability.

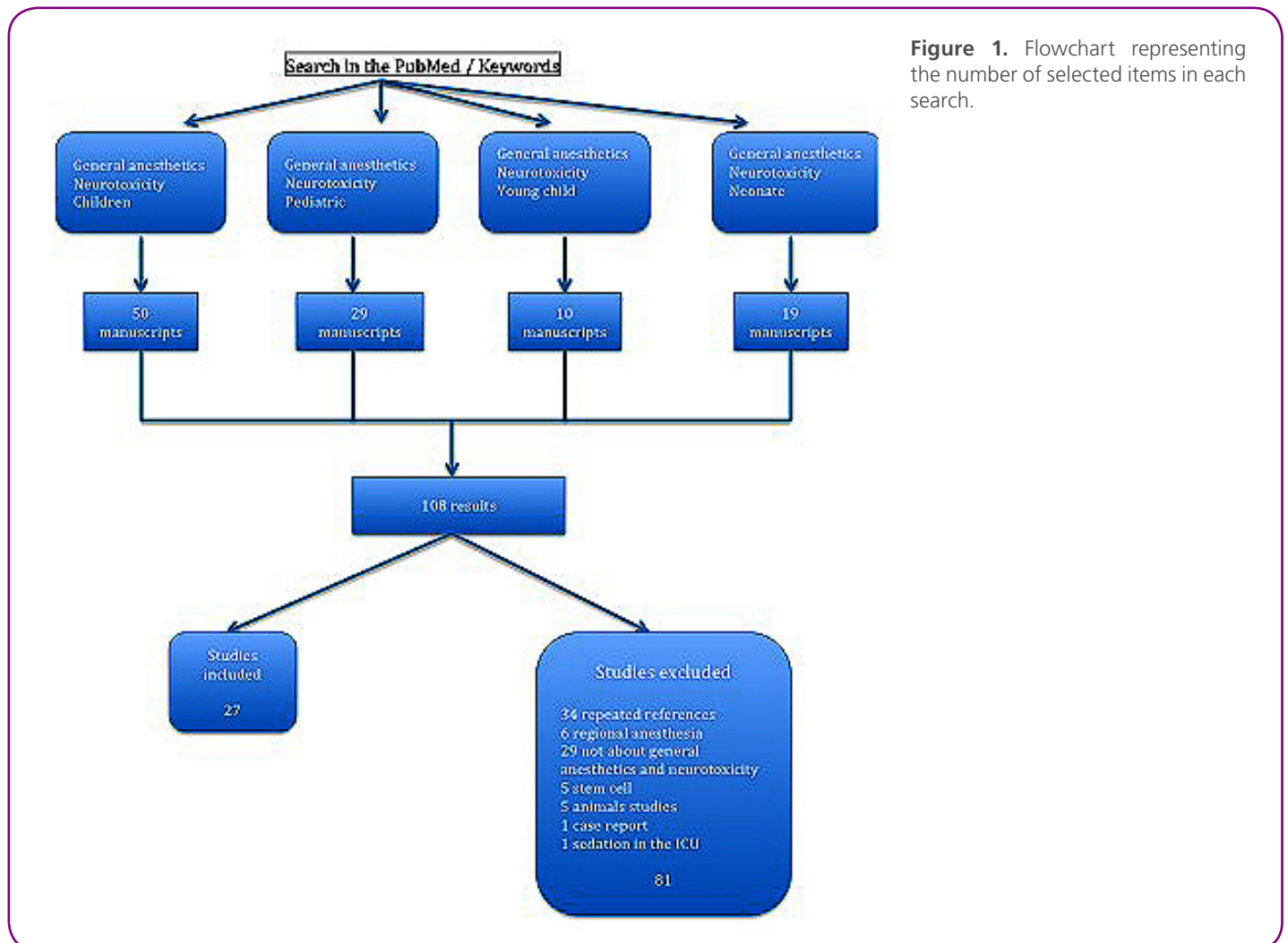


Figure 1. Flowchart representing the number of selected items in each search.

Mechanisms of neurotoxicity

General anesthetics induce neuroapoptosis. This effect is observed especially when there is the use of associated agents that act at different receptors, GABA_A and NMDA. [9] Another associated factor is the exposure in periods occurring more intense activity of neuronal development, as synaptogenesis, resulting in memory and learning disorders. [10]

Apoptosis can be induced by several mechanisms with the final pathway as the formation of caspases, main substances responsible for cell death. The intrinsic pathway begins with the reduction of the anti-apoptotic proteins starting from BCL-2 (B cell lymphoma 2), followed by the increase of mitochondria permeability and cytoplasmic release of

cytochrome C and consequently, caspase-9 and caspase-3, resulting in cell death. [11]

Upon activation of the intrinsic pathway, there is the formation of the death-inducing signaling complex (DISC), with activation of caspase-8 and caspase-3, followed by cell death. [10]

There are two other important pathways in the outcome of neurocognitive disorders after general anesthesia which are: 1- pathway is dependent of brain-derived neurotrophic factor, which leads to induction of Trk-dependent pathway and P75^{NTR} (important inducers of apoptosis). 2- Pathway of neuronal cell destruction that results in decreased density of neurons in specific regions of the cerebral cortex. [10-12]

Table 1: related articles

Authors	Journal	Sample	Main findings
Sinner B. et al. 2014	Anaesthesia	Review article	Animal studies suggest strong evidence of neurotoxicity of general anesthetics. Moreover, this data can note be extrapolated to human.
Bartkowska-Sniatkowska et al. 2014	Anaesthesiology Intensive Therapy	Review article	
Yan J. et al. 2014	J Neurosurg Anesthesiol.	Review article	Evaluated in the literature, the neuroprotective, neurotoxic and anti-inflammatory effects caused by ketamine administered in various doses and in the presence and absence of the noxious stimuli.
Garcia Guerra G. et al. 2014	Paediatr Anesth	Cohort of 91 children under 6 weeks of age and subjected to cardiac surgery.	The use of chloral hydrate was associated with poorer performance on the intelligence quotient test and the use of benzodiazepines resulted in lower scores on visual and motor integration test.
Olsen E.A. et al. 2013	Curr Opin Anaesthesiol	Review article	Evaluates retrospective studies in children under 3 years children exposed to anesthesia and associates them to greater risk of learning disorders after repeated exposure. However, points out that the current data are insufficient to change the current practice
Davidson A et al. 2013	Clin. Perinatol	Review article	General anesthetics in animal models are responsible for accelerating the neuroapoptose, however, there is insufficient data to extrapolate these data to humans. Evidence suggests that the inadequate treatment of pain leads to intense stress and neurotoxicity.
Jevtovic-Todorovic V. 2013	Mol. Neurobiol	Review article	Reaffirms the existing evidence on the neurotoxicity of general anesthetics in animals. And fetches data in the literature to help develop neuroprotective strategies.
Sinner B. et al. 2013	Anaesthesist	Review article	It analyzes the current data highlighting the prospective studies in progress.
Hays SR et al. 2013	J. Urol.	Review article	Repeated exposure to anesthetics and early life result in cognitive disorders.
McCann ME et al. 2012	British J. of Anaesth.	Review article	Discusses the biases associated with retrospective studies and the lack of sufficient evidence to associate anesthetic neurotoxicity
Byrne MW et al. 2012	J Neurosurg Anesthesiol	Review article	Biannual symposia of The Pediatric Anesthesia NeuroDevelopment Assessment research group at Columbia University Medical Center Department of Anesthesiology evaluating new evidence of neurotoxicity.
Vutskits L et al. 2012	Paediatric Anaesth	Review article	Debate studies in experimental animals and clinical studies as well as the limitations of extrapolating the findings to clinical practice.
Vlisides P et al. 2012	Curr Pharm Des.	Review article	Examines current data on neurotoxicity induced by anesthetics and questions the potential implications of this association.
Jevtovic-Todorovic V 2012	Curr Pharm Des.	Review article	Lists the neurotoxic effects of general anesthetics to age, being more likely in the elderly and children during that synaptogenesis occurs

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Authors	Journal	Sample	Main findings
Holtby HM 2012	Future Cardiol	Review article	Describe the causes of neurodevelopmental impairment in children with heart disease
Ward CG et al. 2012	Pharmacol Res	Review article	Neurotoxicity was observed in young animals, however, is not possible to correlate the data to humans.
Bhutta AT et al. 2012	Pediatr Crit Care Med	Randomized clinical trial	Found no evidence of neuroprotection or neurotoxicity in the study.
Thomas J et al. 2011	Anesth Analg	Review article	Evaluates more recent studies of behavioral disorders in children under 3 years following exposure to general anesthetics.
Davidson AJ 2011	Paediatr. Anaesth	Review article	Evaluates the evidence from studies in animals and humans neurotoxicity general anesthetics.
Sun L 2010	British J of Anaesthes	Review article	Assesses the ongoing clinical studies PANDA and GAS.
Brusseau R et al. 2010	Early Human Dev	Review article	Discusses the importance of suppression of responses to stress.
Mons F et al 2010	Ann Fr Anesth Reanim	Review article	Review the safety issues of anesthetic agents on the developing brain..

Clinical evidences

The published clinical studies that were focused on this topic are all retrospective cohorts, with their limitations. The first evaluated a cohort of children under four years old, anesthetized with halothane and nitrous oxide, between 1976 and 1982, and the outcome was the learning disability in mathematics, language or reading. Any of the three were seen as learning disabilities, inadequate clinical situation, as each of these functions is controlled by specific brain regions. [13, 23,24]

Another cohort analyzed children under four years old, who received multiple exposures to anesthesia and surgery and were compared to an unexposed group. A higher incidence of behavioral disorders and attention deficit hyperactivity disorder was found in children who received general anesthesia. [14]

A recent study using the Taiwan database examined 5197 children born between 2001 and 2007

who received single or repeated exposure to general anesthesia and compared to a control group of 20,788 individuals who were not exposed. They sought a possible association between exposure to anesthesia and development of disorders related to autism and found no differences between the groups. [15]

There is a strong association between duration of anesthesia and multiple exposures with learning and behavior disorders. [16]

Study realized with 1143 pairs of identical twins in the Netherlands, with the only variable as the administration of general anesthesia before three years old of age in one of the groups, did not observe any difference in cognitive problems and learning disorders between groups. [16, 17,19]

In Denmark and the Olmsted County, children undergoing surgery using general anesthesia before completing four years old showed no significant difference between groups. [17]

DiMaggio, analyzing a database of the city of New York, has selected 304 children born between 1999 and 2005, submitted to surgical procedures before completing three years old and previously healthy. DiMaggio used as the control group, 10 146 children of the same database that have not gone through surgery and found an odds ratio of 1.7 for the development of behavior disorder associated with anesthesia. [18,21]

There is evidence that the $\alpha 2$ -agonists have anti-apoptotic properties in animal models, decreasing the formation of caspase-3 in the brains of newborn rats, when administered to anesthetized pregnant rodents with propofol. [22,25]

After these findings, even with controversial results in relation to the actual harmful effects of general anesthetics in humans, the FDA (Food and Drug Administration) and the IARS (International Anesthesia Research Society) have established a partnership that created the SmartTots (Strategies for Mitigating Anesthesia- Related Neurotoxicity in Tots). [26]

A team of experts in the matter was gathered and in 2012 they prepared the first agreement to be followed until new studies point more conclusive results. The group met again in 2014 and updated consensus, suggesting the avoidance of surgical procedures in children younger than three years old, except in emergency situations. They added the importance of new studies in animals and randomized clinical trials in the search for more conclusive evidence. [26]

Conclusion

There is currently little evidence and much expectation regarding the neurotoxicity mediated by general anesthetics. Few original articles were published in the last five years; however the topic was widely discussed in some reviews.

At the moment, it is not possible to say that the damage caused by anesthetics in animals can be replicated in humans. However, because of the severity of the outcome, the FDA recommends avoiding anesthesia and surgery in children under three years old, at least in those who are not in an emergency situation.

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