

# General Anesthetics in Children: Neurotoxic or Neuroprotective?

REVIEW

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## Abstract

**Introduction:** general anesthetics are involved in neuroprotection in adults after ischemic events and cognitive impairment. Thus, they also may be associated with learning disorders in children exposed to them before three years of age. Controversial results are found in the current literature. Studies in experimental animals demonstrated a significant increase in neuroapoptosis, however these findings can not be transposed to humans.

**Objective:** Describe about the neurotoxic effects of general anesthetics in experimental animals and children, Highlighting the most recent studies and their impact on clinical practice.

**Method:** This is a systematic review, performed from search in Pub-Med and scielo database, using the keywords "neurotoxicity" and "general anesthetics," and "general anesthetics," "neurotoxicity", "children", "young child "and" pediatric ".

**Results:** The search resulted in 185 articles in pubmed and no articles on scielo. Out of these, 78 met our inclusion criteria. We found that there was a significant evidence of neurotoxicity induced by general anesthetics in experimental animals that were just born, resulting in late and permanent cognitive deficits. This effect was associated with multiple exposures, exposure length of time and combination of drugs. However, some studies found cognitive impairment after a single exposure to anesthetic.

**Conclusion:** There is insufficient evidence to state that general anesthetics are neurotoxic and have the potential to trigger learning and behavior disabilities in children. However, we suggest caution in indicating surgery in children under three years old, analyzing risk-benefit and inserting the family in the decision process.

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## Keywords

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## Introduction

The anesthetic practice has evolved significantly with the emergence of new drugs and techniques and development of monitoring devices, which have allowed the realization of more complex procedures in patients with various comorbidities. [1, 2]

The recommended, until a few years ago was that general anesthesia would be a state of insensibility and chemically induced unconsciousness, propitiated for the performance of surgical or diagnostic procedures and at its end, people returned to their previous state, without any deficits from a physiological point of view [3-6].

However, recent studies in experimental animals suggest the possibility of cognitive disorders, learning difficulties and behavioral changes that go beyond the perioperative. These results still cannot be transferred to humans. However, clinical studies are underway to try to clarify this issue. Some clinical trials and retrospective cohort studies have been or are being completed [6-9].

These changes are more intense after multiple exposures, prolonged exposure and development stages where occurs a steeper synaptogenesis [10, 11].

Therefore, considering that studies show a direct association between exposure to anesthetics and language disorders, abstract reasoning or behavior, we attempted to describe about the neurotoxic effects of general anesthetics in experimental animals and children.

## Method

This is a systematic review, conducted from searching on PubMed database and Scielo, through two independent searches, the first search in the pubmed used the keywords "general anesthetics," "neurotoxicity", "children", "young child" and "pediatric". The second search in the scielo used the keywords "neurotoxicity" and "general anesthetics". Both with the aim of covering

existing research in humans, experimental animals and stem cells. The research was carried out by two independent researchers, who analyzed the articles in isolation and discussed the results below.

Having as inclusion criteria: articles from the last five years; original articles with full access or access to summaries and; based on clinical studies in children and experimental animals, and articles in english language.

In this search we excluded the articles that dealt with studies in that focus on side effects of other substances on the central nervous system such as alcohol, anticonvulsants, opioids, etc. or factors linked to the environment. Articles in languages other than English were excluded from the research.

Then, the researchers met, discussed and selected within the criteria, the articles considered relevant, making a total of 78 articles. **(Figure 1)**

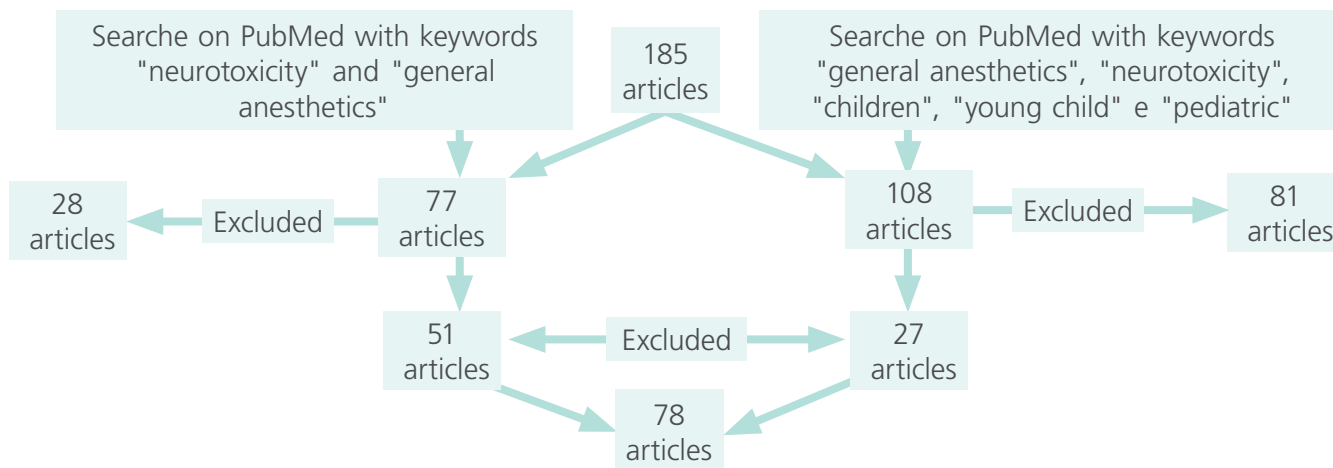
## Results

The search resulted in 185 articles, where 108 about neurotoxicity in humans and 77 articles encompassing the topic neurotoxicity in experimental animals and stem cells. After the exclusion criteria were applied, 78 relevant articles remained, 51 on neurotoxicity in experimental animals and 27 on neurotoxicity in humans. **(Figure 1)**

The results demonstrate that the general anesthetics present neurotoxicity when administered to experimental animals at early stages of neural development, however, human studies are inconclusive and controversial, since some studies showed no association between exposure to general anesthetics and cognitive disorders in humans.

Most studies in experimental animals associate neurotoxicity to the administration of general anesthetics at early ages, where neural development is not yet complete. This effect results from elevation of caspases 9 and 3 and increase in intracellular calcium, triggering cellular apoptosis.

**Figure 1:** Searches performed on PubMed, with filter for the last five years, involving studies in experimentation animals and related to exposure of human children to general anesthesia. Brazil, 2015.



**Table 1.** Articles resulting from the second search where the keywords used were "general anesthetics", "neurotoxicity", "children", "young child" and "pediatric".

Author	Year	Periodic	Method	Results
Bartkowska-Śniatkowska A	2014	Anaest Intens Ther.	Review	The current data are sufficient to delay elective procedures until the age of 3 years old.
Sinner B	2014	Anesthesia	Review	Current data are inconclusive. Further studies should be conducted
Yan J	2014	J Neurosurg Anesthesiol	Review	Ketamine has neurotoxic effect when administered in the absence of noxious stimuli, but has neuroprotective properties when applied in the presence of stimuli.
Olsen EA	2013	Curr Opin Anaesthesiol, 2013	Review	Addresses the MASK, PANDA and GAS study and suggests avoiding changes in current practice and new assessment after completion of these studies.
Garcia Guerra G	2014	Paediatr Anaesth	Prospective cohort	Out of 135 participants, 91 concluded the study that resulted in a lower performance on IQ tests. 95% CI = 1.96 with p = 0.03
Davidson A	2013	Clin Perinat	Review	Studies in animals have shown cognitive disorders associated with early exposure to general anesthetics, however, to provide adequate analgesia and hypnosis are more important than the induced neurotoxicity.
Jevtovic-Todorovic	2013	Mol Neurobiol	Review	Current evidence suggests a strong association between exposure to general anesthetic before 4 years of age and cognitive impairment of long duration.
Sinner B	2013	Anaesthesist	Review	Studies linking exposure at early ages to general anesthetics showed controversial results. Ongoing studies such as GAS and PANDA may bring new perspectives on this topic.
McCann ME	2012	Br J Anaesth	Review	Animal studies are contradictory and in humans are based on retrospective cohorts using old data. Further studies should be conducted so that we could come to some conclusion.
Hays SR	2013	J Urol	Review	Current studies are contradictory. New evidence must be sought.

Author	Year	Periodic	Method	Results
Byrne MW	2012	J Neurosurg Anesthesiol	Review	It is focused on the need for further discussion among anesthesiologists and surgeons in an attempt to arrive at an agreement for the best time for surgery, checking the risks and benefits of the procedure.
Vutskits L	2012	Paediatr Anaesth	Review	Analysis of existing data in the literature and consideration of the pros and cons of indicating surgery in children under three years old.
Vlisides P	2012	Curr Pharm Des, 2012	Review	Review addressing the methodological aspects used and the weaknesses of the cohort studies and questioning whether the findings are sufficient for a change in clinical practice.
Jevtovic-Todorovic V	2012	Curr Pharm Des	Review	Review covering animal and human studies, putting to evidence the data about the association between exposure to general anesthetic at early age and the development of behavioral dysfunction and cognitive impairment
Ward CG	2012	Pharmacol Res	Review	Emphasizes the importance of anesthesia and the deleterious effects of pain. It also discusses the neuroprotection role of anesthetics in ischemia situations.
Thomas J	2011	Anest Analg	Review	Evaluates clinical studies, especially those involving twins and discusses the controversial results of these studies.
Bhutta AT		Pediatr Crit Care Med	Randomized clinical trial	Found no difference with respect to cognition among patients undergoing cardiac surgery who received ketamine during the procedure compared to placebo.
Davidson AJ	2011	Paediatric Anaesth	Review	Points out the impossibility of translating the results of animal studies to humans when addressing exposure to general anesthetics at early ages.
Sun L	2010	Br J Anaesth	Review	Addresses the ongoing studies, PANDA and GAS study, stressing that there is no possibility of translating the results of animal studies prior to disclosure of the findings of these studies, they are expected for 2015 and 2017
Brusseau R	2010	Early Hum Dev	Review	Reviews the current consensus and highlights that the findings should not be translated into urgency and emergency surgeries. One must weigh the risks and benefits of performing or not the procedure and the exposure to anesthetics.
Mons F	2010	Ann Fr Anesth Reanim	Review	It covers the performed studies and concludes that it is not possible to extrapolate the data to current clinical practice. More studies need to be performed
Yu D	2013	J Anesth	Review	Discusses the current findings and suggests that the results are controversial and more studies need to be performed.
Dong C	2013	Toxic Lett	Review	Specifically addresses the studies dealing with the neurotoxicity induced by ketamine and estimates future prospects.
Vutskits L.	2012	Paediatr Drugs	Review	It addresses the current evidence and concludes that there is insufficient data so that we can extrapolate the existing data to clinical practice.

Author	Year	Periodic	Method	Results
Persson J	2010	Curr opin Anaesthesiol	Review	It proposes a new look at an old drug. It covers the side effects and benefits of the use of ketamine
Bakri MH	2015	Saudi J Anaesth.	Cohort	More than one exposure to general anesthetic before the age of 3 years is associated with cognitive disorders, deficits in motor development and behavioral disorders.
Sanders RD	2013	Br J Anaesth	Review	Reviews the current literature, it discusses the limitations of cohort studies and suggests waiting for data from ongoing studies: GAS MASK and PANDA study.

In addition, there is a strong questioning regarding the strength of evidence of the studies, considering these studies are retrospective cohorts and based on questionnaires given to relatives or teachers of children who received general anesthesia before 3 years of age.

Two clinical studies are currently underway to try to elucidate this issue, the PANDA study and the GAS study. The initial results are not conclusive.

## Discussion

There is significant evidence of neurotoxicity induced by general anesthetics in recently born experimental animals, resulting in late and permanent cognitive deficits. This effect was associated to multiple exposures, exposure length of time and combination of drugs. However, some studies found that there was cognitive impairment after a single exposure to anesthetics. [12, 21, 22]

Almost all anesthetics were involved when administered to individuals in phases where there is neural development and synaptogenesis, except for some adjuvants such as  $\alpha$ 2-agonists. [13-15, 21] Some studies suggest that dexmedetomidine administered as a preanesthetic medication possesses a neuroprotective effect, reducing the neurotoxicity induced by propofol and isoflurane. [16, 21, 25]

The mechanism by which local anesthetics trigger its neurotoxic effects involves induction of apoptosis, which starts with the increased conductance of the calcium channels, with an increase of

the intracellular concentration of this, production of reactive oxygen species and release of cytochrome c into the cytosol, culminating with the induction of caspases formation, decrease of the expression of anti-apoptotic proteins (Bcl-2) and increased expression of pro-apoptotic proteins (BAX), inducing acceleration of programmed cell death. [5, 17, 26]

Anesthesia and surgery on their own induce the release of cytokines, especially IL-1 $\beta$  and IL-6, as well as the factor of tumor necrosis) TNF- $\alpha$ , triggering a proinflammatory state that contributes to post-operative cognitive disorders. Lidocaine administered systemically has anti-inflammatory properties and may prove to be an adjuvant to mitigate these deleterious effects. [18, 26]

Another mechanism implicated in neurotoxicity is a dysfunction in the regulation of production and release of neurotrophins. Brain-derived neurotrophic factor (BDNF) modulates, at least in part, the apoptotic cascade. It operates in two types of receptors, the Trk, expressed in normal conditions and that promotes proper homeostasis and synaptogenesis and the p75NTR receptor which has a higher binding specificity to the BDNF precursor (pro-BDNF). [19]

Consequently, there is an accumulation of pro-BDNF in the synaptic clefts with higher binding to p75 NTR receptors, which leads to caspase-3 activation, decreased formation of dendrites and apoptosis. The inhibition of BDNF formation by the anesthetics (especially propofol and isoflurane) also acts indirectly in the neural cell cytoskeleton, pro-

moting the destabilization of the actin, one of its structural components, and reducing its survival. [20]

The GABA receptor activation in immature neurons culminates in increased conductance of calcium across cell membranes. The higher calcium influx causes mitochondrial disorder causing neuronal dysfunction and cell death. [21, 22]

The result of these studies has raised questions and concerns regarding the safety of administration of general anesthesia in children in development phase and in the conduction of pregnant women during childbirth and surgical complications during pregnancy. Some questions were answered; however, most are yet to be elucidated. [12, 23]

Several epidemiological studies have implicated the exposure to general anesthetic in early stages of life as responsible for a higher incidence of learning disorders. This effect was more evident after multiple exposures. [7, 24, 25] Other studies have found no significant differences. [8, 10, 26,]

A retrospective cohort study conducted at Mayo clinic examined the presence of learning disabilities in children submitted to surgery before completing four years old. A higher presence of learning disabilities in children who received two or more surgical procedures under general anesthesia was found, when compared to the group that did not undergo any intervention. [22, 27]

Bartels, using data logging of identical twins from the Netherlands, where one had been submitted to surgery and the other did not receive the intervention, found no difference in cognitive performance between the two groups. [22]

DiMaggio evaluated patients undergoing a single surgical procedure before the age of three and found deficits in language and cognition in children exposed, when submitted to assessment when they were 10 years old. [28]

Wilder evaluated the medical records of the sample made up of preschoolers born in Olmsted County, Minnesota, born between 1976 and 1982 and

divided into three groups: not exposed to general anesthetics before three years old, one exposure and two or more exposures. His study evaluated whether exposure to general anesthetic for termination of pregnancy could lead to the development of cognitive or learning disorders and he found no correlation. However, it concluded that the combination of two or more procedures under general anesthesia or procedures lasting more than 120 minutes in children under four years of age had strong correlation with learning disabilities. [28]

Despite strong evidence found in laboratory, these findings cannot be transposed to the human species, requiring new experimental and clinical studies for a more convincing definition of the neurotoxic effect of general anesthetics in children. [1-5, 12, 15, 21, 29]

## Conclusion

Even with inconclusive results, the issue is of great concern to professionals and family members involved in pediatric patient care, mainly due to the increasing number of surgeries performed on neonates and younger children today.

Therefore, there is not enough evidence to state that general anesthetics are neurotoxic in humans and have the potential to trigger learning and behavior disabilities in children. However, we suggest caution in indicating surgery in children under three years old, analyzing risk-benefit and inserting the family in the decision process until the results of new studies underway show enough evidence to change clinical practice.

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