

Effects of anesthesia on children's brain development

Summary

Nowadays, the administration of most of the anesthetics is being questioned. The quality of reversibility of these medications is being questioned, especially when administered to children under 3 years old. The administration of isoflurane elevates intracellular calcium levels which are critical for cell damage resulting in apoptosis. The NMDA and GABA receptors are indirectly involved in the effect of immature brains. The immaturity of the central nervous system associated to the administration of anesthetic agents such as inhaled anesthetics, ketamine, midazolam, nitrous oxide, and others, produces important changes in the brain that have an impact in the child's later life. There are two important elements in the neurotoxicity of anesthetics, dosage and time administration. Repeating anesthetics produces more brain changes. These modifications have resulted in serious behavioral and memory changes in experiments in animals. It is suspected that a similar situation may arise in children who manifest learning disabilities in later stages.

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Introduction

The fundamental premise for the administration of any anesthetic drug is its character of reversibility, implying that the brain, spinal cord, and peripheral nerves are anatomically and physiologically the same before and after the administration of any anesthetic used. Millions of anesthetic procedures are performed every day worldwide with an accepted level of safety, especially when we talk about the administration of anesthetics in newborns with immature or underdeveloped nervous system. The newborn brain develops in the last trimester during pregnancy inside the uterus and continues its development the first 2 years or extrauterine life. There's evidence that some anesthetics administered at clinical doses to these children produce neurodegeneration in immature brains. The evidence is stronger in newborn rats receiving isoflurane, midazolam, and nitrous oxide. Current evidence associates learning and memory disabilities in later stages in live in lab animals. Most recent studies can't be confirmative because of its inherent limitations, and possible nervous system damage can't be discarded completely.

The strongest strategy to limit this damage is based on the use of neuroprotective measures such as local anesthetics. Regional anesthesia techniques are strongly recommended. However, it is important to remember that anesthetics are just a part of the anesthesia technique that a newborn or infant receives during surgery. It leaves to the known if mechanical ventilation, neonatal intensive care unit hospitalization, blood transfusions, hypoxia, of hypoglycemia could also affect the brain.

Normal brain development in humans

Brain development takes place during a human's first stages of formation. In this period the brain is more vulnerable to the changes produced by anesthetics and other toxic substances. During this stage neurogenesis, gliogenesis, and synaptogenesis (formation, birth, and creation of synapses) happen at a very high rate through the processes of migration, synapse formation, differentiation, and maturation of brain cells. The mechanisms through which anesthetic agents induce accelerated apoptosis and changes in dendritic morphology aren't clear, but they have been attributed to reduced synaptic activity on the effects of excitotoxicity after the regulation of the N-methyl-D-aspartate (NMDA) receptor, since it is the most important brain neurotransmitter acting mainly in the activation of

receptors, because this neurotransmitter contributes essentially to neurogenesis. The mechanism includes the inhibition of the NMDA receptor and the excitation of the GABA receptor, apart from other lesser known receptors. Since ketamine is a non-competitive antagonist for the NMDA receptors that blocks the ligand-activated channels of NMDA, it is one of the agents that produces more brain damage. Other important receptor intervening in neurogenesis is the GABA receptor. This substance acts as an excitatory neurotransmitter in immature neurons. The activation of GABA receptors generates action potentials, which directly open the voltage-dependent calcium channels and increases the intracellular calcium concentration in the hippocampus and other brain structures. This study is supported by the evidence that isoflurane could increase calcium entrance through the voltage-dependent calcium channels. The increase in the levels of intracellular calcium is critical for cell damage resulting in apoptosis and neuronal damage.^{1,2} This means that NMDA and GABA receptors are indirectly involved in the activity balance and therefore in the generation of trophic factors that manage differentiation, growth, and brain apoptosis in immature brains.

At the end of the third month of pregnancy the brain is composed of approximately 125,000 cells, at birth the number of neurons is approximately one billion, which means that in a relatively short period there have been thousands of cell divisions. The human brain doubles its size in the first year of life and reaches 90% of its maximum size by the age of six, only the lower part of the nervous system is fully developed (brain stem and spinal cord) while higher regions (limbic system and brain cortex) are immature. All the neurons in the brain cortex are created before birth, but they are poorly connected and most of their synaptic connections are developed after birth. During this period it is estimated that the highest amount of synaptic formation in the brain cortex is of 2 million neurosynapses per second. At 2 years of age the brain cortex will have hundreds of trillions of synapses working. This means that the brain continues to develop after birth.³ The stages of brain development are divided in neurogenesis and proliferations, differentiation, synapse formation, and myelination. The number of synapses is at its highest during infancy and declines after it. In the human brain the synaptogenesis starts during the last trimester of pregnancy and it is believed to end during the second or third years of life.⁴ Neuron loss occurs via apoptosis. Apoptosis or "cell suicide" is an energy consuming organized process through which undesired cells are removed from the organism. Multiple factors

may trigger apoptosis including normal growth and development. Some diseases, anesthetics, and toxic substances for the brain such as alcohol and antiepileptic drugs are well-known examples to this day. The second important process is brain myelination, occurring in post-natal life. The newborn brain contains very little myelin and bad nutrition contributes to poor myelination in the newborn. Myelination is completed approximately at the age of two.

Evidence of brain damage in experimental animals

Many studies have shown apoptosis acceleration in newborn mice after being exposed to anesthetics such as ketamine, propofol, nitrous oxide, inhaled agents like sevoflurane, isoflurane, and desflurane or benzodiazepines such as midazolam. The use of sevoflurane 2.5% for a 2-hour anesthesia, in the 14th day of gestation in pregnant mice produces immediately an increase in apoptosis in its offspring and subsequently damages learning and memory in newborn mice as they grow. Interestingly, 4-hour exposure of sevoflurane at 1 MAC for administration causes important problems in mice. Also 6-hour exposure to desflurane at doses of 7.4-8%, or 0.75 – 2.0% isoflurane, or 1.1 – 3.0% sevoflurane, all dramatically increase cortical neuron apoptosis in the next 6 – 8 days postpartum. It seems that all inhaled anesthetics used produce a certain level of apoptosis at equal potency. Isoflurane causes more neuroapoptosis than sevoflurane or desflurane. In adult mice treated with 8% desflurane, 3% sevoflurane, or 2% isoflurane for 6 hours, the anesthetics produced memory damage at long term. None of these anesthetics produced emotional abnormalities or anxiety. In mice that were small for their age treated with 6 hours of isoflurane 0.75% or sevoflurane 1.1% there was no evidence of memory damage. Contradictory results have been found with increase in apoptosis in the hippocampus neurons in the offspring of the study mice, with learning and memory damage.⁵

Other studies have proven that very young mice with multiple exposures to sevoflurane induce cognitive damage by the age of one month, this was associated to the high levels or pro-inflammatory markers at the end of a 3-day administration of the inhaled anesthetics. Recently the neuroinflammation induced by anesthetics has been suspected as the possible mechanism for the cognitive impairment in newborn mice. It seems that some young rats exhibit cognitive damage or neuroinflammation. It's evident that the damage produced to these mice depends on the frequency and duration of the exposure to the inhaled anesthetics. One dose of any of the inhaled anesthetics is not necessarily associated to higher rates of apoptosis or neuroinflammation.⁶ Propofol administered at 75mg/kg to 7 days-old rats has caused cell death in brain cortex and hippocampus, its daily administration for 7 consecutive days has resulted in marked damage in neuroapoptosis and a significant reduction in neuronal density. The same occurs in terms of learning and memory. The long term learning damage and memory problems are associated with a low level of brain neurotransmitters, glutamate in cortex and hippocampus of adult rats.⁷ Most of the knowledge of the toxic effect of anesthetics has been gathered from lab mice, but recently the data has migrated to other primates like monkeys. It's been proven that ketamine or propofol exposure during 5 consecutive hours in rhesus monkeys produces an increase in glial apoptosis. Exposure to 70% nitrous oxide with 1% isoflurane during 8 hours at 5 or 6 days of age, has caused neuronal apoptosis and temporal cortex necrosis (gyrus and hippocampus), situation that doesn't replicate when both anesthetics are used on their own and on low dosage. It's important to mention that the dosis used for ketamine in this study was 20 – 50mg/kg/hr, much higher than the one used on clinical practice. This makes it possible that the effects of anesthetics are dose-dependent.

Clinical evidence on humans

It's been known for years that the use of alcohol during pregnancy has serious neurotoxic consequences for the fetus's brain, called fetal alcoholic syndrome, characterized with microcephaly, epileptic convulsions, behavioral abnormalities and cognitive deficits. GABA agonists and NMDA receptor antagonists may trigger apoptosis exponentially. Several studies have proven the association between mayor neonatal surgery, cardiac surgery, esophagus atresia repair, laparotomy or hernias, which have been correlated with poor neuronal development when compared with healthy children controls not submitted to anesthetic agents.⁸ Children submitted to correction of esophagus atresia during the neonatal stage have experienced learning problems and behavior disorders in the following years, remembering that many of these children were premature, thereby presenting other congenital defects, originating longer neonatal intensive care units hospitalizations and possibly multiple anesthetic episodes. Thereby other variables must be taken into account. Neonatologists have also reported similar findings.⁹

In a cohort study, Wilder et al.¹⁰ studied children under 4 years of age submitted to neonatal surgery and proved that learning problems were directly related to the number of surgeries performed. This study was strongly proven when chronic diseases and multiple surgeries were analyzed separately. Multiple exposures to anesthesia increase the risk of learning disorders, the higher the number of exposures the risk of learning problems increased proportionately. The children exposed to only one surgery and anesthetic act didn't show evidence of learning problems.¹⁰ Di Maggio et al.¹¹ examined cohort of children less than 3 years old subjected to hernioplasty under general anesthesia. These children had twice the risk of developing learning disabilities, behavioral disorders, autism, and language and speech impairment. Boys were more affected than girls. The study didn't evaluate the time, duration, and frequency of exposure to general anesthetics. Behavioral disorders were diagnosed three to four years after exposure.¹¹ Another very similar study in Australia, where they studied the association between one single exposure to general anesthesia in children under 3 years old, and later when they were 10 years old they studied the neurocognitive development of these children. They found a significant impairment in language and abstract thinking.¹²

There are three key factors in the effects of anesthetics in children under 4 years old. The first one is the moment of drug exposure and the child's age. It's proven that neurological damage is highly dependent of the stage of brain development. It seems that neurons are especially vulnerable during the period with the highest rate of neuronal reproduction. This period varies within species. In rats this period is found between the 7th – 10th day of life, in rhesus monkeys it is found between the 5th and 16th day of life. In the human brain this period seems to be found between the last trimester of pregnancy until the 3rd years of life. The maximum period of synaptogenesis is different for different types of brain cells, which makes different susceptibility to the anesthetic possible, depending on the species.

Another important factor is the frequency and time of exposure to the anesthetics. In animals a direct link has been proven for duration, exposure, and apoptosis induction in vivo as well as in vitro. A single dose of anesthetic is not necessarily associated with neuronal damage. Multiple exposures to surgeries and general anesthetics increase the risk of learning problems. Two episodes of surgery and general anesthetics increase the risk of learning problems. Two episodes of surgery and anesthesia in a study with 100 patients presents a risk ratio (RR) of 1.59 (95% CI; 1.06 – 2.37), with three anesthetics and

surgeries in a sample of 44 patients the RR was of 2.60 (95% CI: 1.70- 4.24). The risk of learning problems increases as the number and duration of anesthesia events increases. The aforementioned data shows that neuronal apoptosis increases directly with the duration of repetition of anesthetics.

A single dose of ketamine in immature brains does not induce apoptosis, in contrast with its repletion or duration. Each of the anesthetics has a time limit to produce neuronal damage and each species is different. The limitations of this study include: patients older than 4 years old, very few patients less than a year old, and the fact that 67% of the patients had their first exposure to anesthetics after their first year of age. Ninety percent of the children studied received anesthesia with halothane and nitrous oxide without oximetry or capnography, monitoring parameters that today are considered essential.¹³ The last factor is the necessary dosage to produce toxicity. It's clear that by increasing the dose the number of neurons affected increases, many examples confirm this. For example, isoflurane during 5 minutes in 4 consecutive days in young mice produces memory impairment.

Recommendations

In the US, more than one million children under 4 years old receive annually general anesthesia for necessary surgical procedures. Most children seem to recover brain functions completely to an acceptable degree. Until proven otherwise, it is advisable to maintain duration of surgery and anesthesia as brief as possible, using short-acting medication on a combination of general anesthesia with regional anesthesia. Inhaled anesthetics are the most studied in terms of neurotoxicity, especially isoflurane. Isoflurane has been implicated in the antagonism of NMDA receptors and agonism of GABA receptors. This agent's neurotoxicity is dose-dependent, producing cell death, especially in the dentate body and the olfactory bulb, sites which continue to develop during early development. There's evidence that xenon with isoflurane may diminish brain damage deficit.^{14,15}

Long term results with sevoflurane seem similar to those of isoflurane, nevertheless short term memory seems not to be affected. Desflurane exhibits effects similar to isoflurane and sevoflurane. In the NOPAIN study, the neurotoxicity of midazolam was evaluated in three groups. In the control group 24% of newborns presented poor neurological development, 32% of the midazolam group and 4% in the morphine group. There were no significant differences in the neurological results. Several studies have associated ketamine use with apoptosis damage in developing brains. The apoptosis induced by ketamine has been proven to be dose-dependent.¹⁶ Nitrous oxide, midazolam, and isoflurane are the principal promoters of brain damage in 7 days old rats.¹⁷ Propofol has been one of the least studied medications for brain damage in immature rats' brains. However, in Rhesus monkeys, similar changes have been observed with isoflurane, a phenomenon seen after 5 continuous hours of administration for 4 to 5 days. This has led us to believe that intravenous techniques with propofol should be avoided at these ages in children until better long term results appear.

As we can see most of the anesthetics used today in clinical anesthesiology are capable of producing secondary damage, most of them at long term when the brain has stopped developing. Avoid prolonged exposure to inhaled anesthetics and preferably use modern anesthetics. Special attention is required for those children receiving multiple surgical procedures. There's a variety of compounds such as lithium, melatonin, L-carnitine, dexmedetomidine, and xenon which have displayed neuroprotective properties, although their mechanisms aren't clear yet.¹⁸⁻²⁰ It's undeniable that in light of current information

available there are many questions still unanswered, only a few have been answered. During many years we used anesthetics without knowledge of their long term effects. Today, research forces us to be more selective and careful in our practice.

Conclusion

Anesthesia is not an end in itself. It is a necessary and indispensable procedure for the surgical act. Avoiding it is not ethical. It's indispensable and necessary in light of current knowledge. Findings in human beings aren't conclusive enough to illustrate the neurotoxic effects in the brains of children under 3 years old. Prospective studies are needed to determine definitive changes in developing brains. In daily practice a short duration of anesthesia is advisable, with multimodal pain treatment, avoiding severe hemodynamic changes like hypotension, hypocapnia, hypoglycemia, and hypothermia, since these changes can also affect neurological development. Lastly, avoid using the same anesthetics in several procedures.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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