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REVIEW ARTICLE

Anaesthesia in early childhood – is the development of the immature brain in danger?

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Abstract

Experimental studies performed on immature animal brains had demonstrated a neurotoxic effect following sedation and general anaesthetics administration. The same magnitude of neurotoxicity has been suggested but not been proven to neonates, infants and small children who have undergone anaesthesia. There is a justified and increasing inquiry regarding the administration of general anaesthesia to paediatric patients.

Keywords: neurotoxicity, general anaesthetics, developing brain, childhood

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Introduction

General anaesthesia is a complex pharmacological response following the administration of different classes of drugs acting at multiple levels of the central nervous system. The mechanism of general anaesthesia is still not completely understood, but the procedure is considered safe, being widely used regardless of age and co-morbidities.

However, increasingly research carried out on animal models, but also certain human retrospective clinical data suggest the presence of neurotoxic, pro-apoptotic and neurodegenerative consequences following the administration of general anaesthetic drugs, mainly manifested by long-lasting neurocognitive deficiencies, memory and learning impairment [1-5].

In this review, we aimed to briefly discuss the newest achievement related to anaesthesia-induced neuronal toxicity and subsequent neurobehavioral and cognitive disturbances, with special emphasis on the developing brain.

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Preclinical evidences of anaesthesia-induced neurotoxicity

The most complex networks of the central nervous system are a consequence of neuronal proliferation, differentiation, synaptogenesis and rapid development of dendrites. These physiological processes characterize the most intensive periods of brain development during the perinatal life and early childhood [6].

Early studies in foetal and neonatal rats demonstrated that anaesthesia has similar effects to the effect of alcohol on the human foetal brain, a strong and widespread neurodegeneration through apoptosis, mechanism which implies N-methyl-D-aspartate (NMDA) receptor antagonism and γ-aminobutyric acid ($GABA_A$) receptor potentiation [1, 2, 6]. As a result of these preliminary findings, a large number of subsequent researches were conducted, aiming to investigate the individual or combined anaesthetics-induced neurotoxicity and to understand its intimate mechanisms of occurrence. A *Pub Med* search for studies investigating the neurocognitive impact of anaesthetic drugs on children indentified more than 8000 papers, about 1000 of which have been published since 2013, but it

should be noted that nearly all were conducted on various animal models [7]. Data from animal experiments have strongly indicated that anaesthetics commonly used in the clinical practice can induce neuronal apoptosis and impairment of normal synapse development and conformation. These effects can later result in substantial brain and behavioral abnormalities in mice, rats, guinea pigs and nonhuman primates [8-11].

Regarding the neurotoxic potential of more commonly used inhalational anaesthetics administrated during gestational period in mice, a 6-h exposure to equipotent doses of desflurane, isoflurane and sevoflurane, dramatically increased neocortical neuronal apoptotic cell death in the first postnatal days [12-13]. Among the inhaled anaesthetics, desflurane demonstrated the greatest levels of neuroapoptosis; during the mice adulthood life, all three anaesthetics impaired the long-term memory, but only desflurane caused the most significant impairment in short-term spatial working memory [13]. In contrast to mice, in rats a single sevoflurane exposure during the neonatal period can result in a similar neuroapoptotic effect, significant impairment of both short-term and long-term memory but not persistent neuronal loss and behavioral retardation at later age [14]. Postnatal, a multiple exposure to sevoflurane or isoflurane in young mice and rats was associated with a significant increase in the levels of pro-apoptotic inflammatory markers [15], long-term memory impairment [16] and cognitive impairment correlated with persistent decrease in the hippocampus neural stem cell pool and neurogenesis [17]. Nitrous oxide is still known as the only inhalational anaesthetic that does not induce neurotoxicity in animal models, when used as a sole anaesthetic, probably due to its primary effect through NMDA receptor antagonism instead of $GABA_A$ receptor activation [2]. However, when compared to isoflurane alone, 75% nitrous oxide added to 0.75% isoflurane increased neurotoxicity, suggesting an additive neurotoxic effect of nitrous oxide when combined with other anaesthetic agents [18]. The earliest animal studies with xenon demonstrated the lack of neurotoxicity when administrated alone, and even an attenuation in neurodegeneration in a dose-dependent manner when it was added to 0.75% isoflurane [19]. Nevertheless, a recent *in vitro* comparative histological study on rats' hippocampal cultures concluded that xenon increased neuronal apoptosis in a similar manner to isoflurane and sevoflurane equipotent concentrations [20]. However, whether these results can be extrapolated to clinical practice remains questionable, because the hyperbaric administration of xenon for clinical anaesthesia is not yet applicable.

Intra-peritoneal repeated administration of propofol to neonate rats resulted in significant neuroapoptosis, followed by significant long-term learning and memory impairment during adulthood, whereas neonate rats that had only a single administration of propofol did not. This cognitive impairment was found to be associated with a decreased level of glutamate in the cortex and hippocampus of the adult rats [21]. Neuronal and oligodentrocytes apoptosis has been also demonstrated in the brains of foetal and neonatal macaque monkeys following propofol administration [22].

Exposure to ketamine causes neuroapoptosis accompanied by significant up-regulation of subunit NR1 of NMDA receptors in rat forebrain neurons culture, a phenomenon that was prevented by pre-treatment with NR1 antisense RNA [23].

Postnatal exposure of rhesus monkeys to ketamine for 24 h induced significant neuroapoptosis identified by histological staining [11]. Neurocognitive assessment with operant test battery following ketamine administration to non-human primates in the first-seven life days showed a long-term impairment of learning and memory, expressed mainly through lower motivation and learning scores [10]. Moreover, administered as a single dose over a prolonged period of 24 hours during a vulnerable phase of brain development, ketamine causes long-lasting deficits of memory and attention in primates [24].

The human evidences of anaesthesia-induced developmental neurotoxicity (AIDN)

The extrapolation of results provided from animal studies to humans remains questionable to a large extent, the more so as there is a lack of prospective human studies and also there is no possibility to demonstrate the neuroapoptosis process by histological or staining investigations. Therefore, the design of studies that could give the reasonable answers regarding the neurotoxicity of anaesthetics in humans will be a real challenge. What we know in humans arise from some retrospective and epidemiological studies.

Wilder et al. [3] retrospectively found, in children exposed at an age under 4 years to two administrations of general anaesthesia, or to more than 120 minutes of anaesthesia, a significantly increased risk in learning disability, defined as low performance on standard achievement tests. If a single exposure did not increase the risk of anaesthesia-induced neurotoxicity (AIDN), the hazard ratio for children receiving 2 anaesthetics was 1.59 and the hazard ratio for those receiving 3 or more was 2.6.

Kalkman et al. [5] retrospectively investigated the neurobehavioral outcomes in children exposed to general anaesthetics during urological surgery between

1987 and 1995, and found that 13% of children exposed to anaesthesia before the age of 2 years developed a behavior disorder, compared with 6% of children who were exposed after the age of two.

In a discordant study made on 1143 monozygotic twin pairs between 1986 and 1995, Bartels et al. [25] showed that exposure to anaesthesia before the age of 3 was not associated with a difference in school performance compared with the unexposed twin.

DiMaggio et al. [4], in another retrospective cohort study made on 383 children who underwent inguinal hernia repair before the age of 3, identified a hazard ratio for AIDN of 1.1 with one anaesthesia and of 2.8 and 4 for 2 and respectively 3 or more exposures.

On the other hand, in a very large cohort study, involving 2689 children who had underwent inguinal hernia repair in infancy, no evidence was found that a single and brief exposure reduced academic performance at the age of 15 or 16 years [26].

In a recent systematic review and meta-analysis, Wang et al. [27], investigating the currently available clinical and epidemiological evidence on the association of anaesthesia with neurodevelopmental outcome in children, concluded that procedures of anaesthesia/surgery before the age of 4 could be associated with a later developed neurological deficit, especially for those with multiple times of exposure.

In another study it was demonstrated that children repeatedly exposed to procedures requiring general anaesthesia before the age of 2 were at an increased risk for the later development of attention deficit-hyperactivity disorders (ADHD) syndrome [28], an observation disputed by a large retrospective subsequent study [29].

Prospective studies on AIDN

Before reaching any meaningful conclusions about the impact of the exposure to anaesthetics on cognitive development, there is a need for better information which can be provided by carrying out prospective human studies. Regarding this need, three important comprehensive studies are currently underway using a prospective large battery of neurocognitive tests.

1. PANDA (**P**aediatric **A**naesthesia and **N**euro**D**evelopment **A**ssessment), an ambidirectional study of children ASA class 1 and 2 before 36 months of age, exposed to general anaesthesia for hernia repair matched to siblings not exposed. The investigated group will be followed up prospectively between the ages of 6 and 10 years in eight involved US centers, by using a comprehensive battery of neurocognitive tests. The pilot study has already been completed and demonstrated the feasibility of such an approach [30].

2. The GAS study (**G**eneral **A**naesthesia **S**tudy), a multi-centre randomized controlled trial involving 29 centers around the world, which aims as a primary objective to compare regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants requiring inguinal hernia repair. Six hundred infants below 60 weeks post-conception age are randomized to receive either general anaesthesia with sevoflurane or spinal anaesthesia without sedation. The follow-up period will be at 5 years, with an evaluation performed at 2 years using a variety of performant neurodevelopmental and neuropsychological tests. The expected date of completion is 2015/2016 [31], but recently published preliminary findings from the GAS study showed that less than 1 hour sevoflurane anaesthesia in infancy did not increase the risk of neurodevelopmental outcome at 2 years of age compared with awake regional anaesthesia [32].

3. The MASK study (**M**ayo **A**nesthesia **S**afety in **K**ids) is also ambidirectional but differs in that it measures comprehensive outcomes at two separate ages (between the ages of 8 and 12 years or 15 and 19 years during the period 2012-2016); it includes children with single and multiple anaesthetic exposures. Selected children participate in a single session of neuropsychological testing. An operant test battery is used, the same used to study anaesthetic neurotoxicity in nonhuman primates. The results of this testing will be compared among children with different anaesthetic exposure histories. The expected result will be a detailed phenotype of possible anaesthetic-associated neurotoxicity in humans. Also, it will represent the first comparison of effects of anaesthetic exposure in children and nonhuman primates performing nearly identical behavioral tests [33]. The study is likely to report first results in 2017.

Summing up the data provided from preclinical and clinical studies, the present knowledge strongly suggests that repeated exposure to anaesthesia and not a single anaesthesia seems to be associated with AIDN – in which learning (reasoning), speech and language performances (but not behavior) are impaired.

Mechanisms of anaesthetic-induced neurotoxicity

The susceptibility of the developing brain to anaesthetic-induced neurotoxicity compared to the mature brain has long been described. In the rodent brain, evidence suggests that this type of injury is age-dependent, peaking at postnatal day 7 (P7), diminishing by P14, and absent by P21 [17, 34]. The vulnerability of the developing brain to anaesthetics depends on the anaesthetic agent concentration (or its toxic metabolites) reaching the developing nervous system, and also on the period of life when the exposure to anaesthetics

takes place. Obviously, general anaesthesia used in paediatric or obstetric medicine meets both criteria. Anaesthetic effects on the brain during its growth spurt period can initiate a cascade of alterations in neurodevelopment which can be detected structurally or functionally [8].

The first studies on the anaesthetic-induced neurotoxicity described multiple mechanisms by which commonly used anaesthetics may promote neuroapoptosis in immature animal brains. The most important mechanisms refer to anaesthetics-induced NMDA receptor inhibition and GABA receptor excitation [35], anaesthetics-induced decrease in neurotrophic factors [36] and anaesthetics-induced mitochondrion dysfunction [37-39]. Any greater or longer inhibition on NMDA receptors of immature neurons stimulates the expression of NMDA receptor subtype one (NR-1), which subsequently allows a greater influx of calcium into neurons, followed by an increase in the generation of reactive oxygen species and neuronal apoptosis [40]. In turn, activation of GABA receptors generates action potentials and, via voltage-dependent calcium channels, increases the intercellular calcium level, a critical factor in excitotoxic cell damage and leading factor to neuroapoptosis [12].

In the immature brain, Ca^{2+} oscillation (defined as periodical increase and decrease of intracellular Ca^{2+} concentration) plays an important role in synaptogenesis, neuronal differentiation, development of neuronal network and plasticity. It can increase CaMK II (calcium/calmodulin-dependent protein kinase II) levels; this will promote neuronal synaptic plasticity and synapsin levels, improving neuronal synaptogenesis [41, 42]. Any dysregulation of intracellular Ca^{2+} homeostasis which interferes with Ca^{2+} oscillation will inhibit neuronal synaptogenesis and leads to neuronal apoptosis.

Excessive intracellular calcium sequestration can increase accumulation of reactive oxygen species inside mitochondria leading to mitochondrial damage. The injured mitochondria may release pro-apoptotic proteins like BAX and cytochrome *c* to cytosol, which initiate apoptotic pathway [37].

Moreover, recent evidence suggested that mitochondria is a subcellular target of general anaesthesia; when administrated during the postnatal period, general anaesthetics may produce mitochondrial morphological disruption and a decrease in their density in presynaptic neurons [38]. Along with morphological changes, general anaesthetics may cause impaired mitochondrial regeneration and dysfunction (particularly in immature neurons), and a very serious disturbance of neuronal scavenging capacity [40]. Administering a radical oxygen species (ROS) scavenger or a mitochondria protector in the peri-anaesthesia promotes mitochondrial integrity, significant down-regulation of ROS and lipid peroxidation, prevention of mitochondrial morphological damage, protection of neuropil and prevention of neuronal loss.

These results suggest that exposure to general anaesthesia during perinatal life and early childhood can impair mitochondrial morphogenesis, integrity and function at the peak of synaptogenesis, and that this mitochondrial impairment may be the primary factor in anaesthetic-induced acute neuroapoptosis and cognitive abnormalities in later life [8].

Recent studies suggest that neuroinflammatory mediators such as cytokines may be also involved in anaesthetic-induced neurotoxicity. The contribution of surgical trauma has been proven in the development of neuroinflammation [43]. At the same time, an increase of the levels of proinflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β in brain tissues was demonstrated after administration of isoflurane [44]. Sevoflurane anaesthesia also increases caspase activation, apoptosis and beta-amyloid (A-β) protein deposition in the brain tissues [45].

Very interestingly, the anaesthetics may also promote neuronal injury in the immature brain by affecting the physiology of neurotrophins. Brain-derived neurotrophic factor (BDNF) – supporting neuronal survival, differentiation and several forms of synaptic plasticity in the developing brain – can be inhibited by the volatile anaesthetic isoflurane [46] or by the intravenous anaesthetic propofol [47], ultimately leading to neuronal apoptosis.

Neuroprotection against anaesthetics-induced neurotoxicity

Since the apoptosis and the impairment of the neurotrophic pathways have been proved to be the most important pathophysiologycal mechanisms in anaesthetics-induced neurodegeneration, it is essential to develop and explore clinically relevant neuroprotective strategies.

In vitro and *in vivo* studies have shown that erythropoietin could have a direct neurotrophic and neuroprotective effect, particularly in conditions of neural damage, such as hypoxia, ischaemia or brain haemorrhage. Also, erythropoietin can influence the release of neuromediators, playing an important role in synaptic plasticity and thereby in learning and memory [8]. At least one study has shown that the administration of erythropoietin prior to 6 hours exposure to isoflurane attenuates neurodegeneration induced by isoflurane in postnatal 7 days mice [48].

Nicotinamide, a water-soluble vitamin coenzyme in a wide variety of enzymatic redox reactions, protects

against ethanol-induced apoptotic neurodegeneration [49] and recently was found to attenuate ketamine-induced apoptosis in the developing rat brain [50]. Nicotinamide is also a potent inhibitor of proinflammatory cytokines, being able to inhibit isoflurane-induced increase in levels of proinflammatory factors TNFα, IL-6, and IL-1β.

Vitamin D3 can also protect against ketamine-induced neuroapoptosis. A preclinical study demonstrated that pre-treatment with vitamin D3 of postnatal days-6 animals prevents ketamine-induced apoptosis in somatosensory cortex. Vitamin D3 can induce calcium binding protein expression or enhance trophic factor action, both of which can stabilize intracellular calcium [51].

Vitamin C, known as an antioxidant, can eliminate oxidative stress and has been used to treat ethanol-induced neurotoxicity; therefore, it may also be effective against anaesthetic-induced neurotoxicity [52, 8].

Dexmedetomidine, as a central α2 adrenoceptor signaller, plays a trophic role during neurodevelopment and is neuroprotective in several settings of neuronal injury. It has been shown that dexmedetomidine, in a dose-dependent manner, can prevent against isoflurane-induced injury in the hippocampus, thalamus and cortex, and long-term memory impairment in neonatal rats. Dexmedetomidine, but not clonidine, exerts its neuroprotection due to its neurotrophic effect, by reducing caspase-3 activation, inhibition of calcium entry, scavenging of glutamate, and reduction in NMDA receptor activation [53, 54].

Recently, it has been demonstrated that preanaesthetic administration of lithium chloride blocks sevoflurane-induced memory impairment, by reversing inhibitory effect of sevoflurane on glycogen synthase-3β (GSK-3β) phosphorylation in the hippocampus of rats [55]. Lithium treatment can also significantly increase BDNF serum levels, and suppress neuroapoptosis in the central nervous system through the BDNF-Bcl2 antiapoptotic signaling pathway [56].

Melatonin, a sleep-promoting agent and antioxidant, demonstrates a neuroprotective effect mediated by inhibition of mitochondria-dependent apoptotic pathway [57]. Other neuroprotectors are also reported to alleviate anaesthetic-induced neurotoxicity in the developing brain [58, 59].

Practical approach of presumed anaesthetic neurotoxicity in humans: should we change the practice?

In the face of growing evidence of anaesthetics-induced toxicity, provided by animal preclinical studies and suggested by human retrospective studies, considering that millions of children receive general anaesthetics each year and that clinicians are frequently faced with the caregiver's questions about the risk of brain damage following anaesthesia, the question is whether and to what extent the anaesthesia practice in children should be modified.

In response to these increasing concerns regarding the potential adverse consequences of general anaesthetics and sedatives administered in children, the Food and Drug Administration (FDA) established in 2009 a public-private partnership with the International Anaesthesia Research Society (IARS), called **S**trategies for **M**itigating **A**nesthesia-**R**elated **N**eurotoxicity in Tots or Smart Tots [60].

In 2012 the FDA, Smart Tots and the American Academy of Pediatrics issued a consensus statement that summarized the state of knowledge and suggested several key recommendations. The main recommendation of the consensus was that anaesthesia for elective surgery should be avoided in children less than 3 years old, apart from emergencies or life-threatening situations. The Smart Tots meeting in June 2014 reviewed the newest collected data from animal and human studies since the release of the original consensus statement. The conclusion of experts was that the current data from animal studies are strongly supportive in order to continue with large-scale clinical studies. The same expert-group reinforced the recommendation that surgical procedures performed under anaesthesia in children less than 3 years old should be postponed unless the situation is urgent. The statement also emphasizes the need to determine whether anaesthetics may cause brain dysfunction in infants, toddlers and small children.

The FDA and Smart Tots propose the notion of large, prospective and multicenter trials intended to clarify certain aspects such as the contribution of trauma surgery and neuroinflammation (acting as separated triggers) to neurotoxicity, the place of less or non-neurotoxic drugs (such as dexmedetomidine) and the place of the local anaesthetic blockade in the anaesthetic plan [61].

In future, clinicians and parents will await clear answers regarding: the most high risk populations to develop neurotoxicity; which type of anaesthetics; what dose or the timing of administration are at the highest risk to induce neurodegeneration; if there are reliable biomarkers for early diagnosis of anaesthesia-induced neurotoxicity; the magnitude of brain damage.

Until now there is insufficient clinical evidence able to modify current anaesthesia practice, to justify changes in usual clinical doses or to jeopardize the clear benefits of general anaesthesia. However, anaesthesia clinicians can make some efforts to simplify the anaesthetic regimen regarding the duration, depth and the possibility to avoid unnecessary drug combinations.

The addition of loco-regional and neuraxial techniques to general anaesthesia offer multiple benefits and also can contribute to reduce the depth of general anaesthesia.

Conflict of interest

Nothing to declare

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Anestezia la copiii mici – este dezvoltarea creierului imatur în pericol?

Rezumat

Rezultatele studiilor experimentale efectuate pe creierele imature ale unor animale au arătat un efect neurotoxic secundar sedării şi administrării de anestezie generală. Un grad similar de neurotoxicitate a fost sugerat dar nu a fost demonstrat în cazul nou-născuților, sugarilor şi copiilor mici care au primit anestezie. Există în prezent o îngrijorare crescândă şi justificată privind administrarea anesteziei generale la pacienții pediatrici.

Cuvinte cheie: neurotoxicitate, anestezice generale, creier în evoluție, copilărie