Chapter 5

Anesthetic Neurotoxicity in Pediatric Patients

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Additional information is available at the end of the chapter

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Abstract

In recent years, an increasing number of publications have shown the negative effects of anesthetics on the developing brain and have made inquiries about anesthesia for pediatric patients in practice. Anesthesia is applied to millions of children for surgery, imaging, and other invasive procedures; the issue is very serious and concerns. In this chapter, experimental and clinical studies about the issue have been summarized. As a result, anesthetic drugs except alpha-2 adrenergic agonist anesthetic (NMDA antagonist or a GABA agonist) used in pediatric patients (especially if there is no painful situation) have potential neurotoxicity. Particularly, if anesthesia exposure was applied in the fragile period (the first 4 years) and if used at higher concentrations or repeated anesthesia application, adverse effects of anesthesia exposure on the developing brain have been claimed. But, the issue is not fully clarified yet.

Keywords: anesthesia, neurotoxicity, neonatal, developing brain

1. Introduction

Since the beginning of the modern anesthesia (nearly 170 years), millions of people have received inhalation anesthetics, intravenous anesthetics, or a combination in order to create general anesthesia. These drugs have been applied in all age groups, from newborns who may be only a few hours old to geriatric patients. In fact, pediatric patients comprise a significant proportion of the total number of patients treated with general anesthesia, a trend that will continue well into the future.

Pediatric patients are not miniature versions of adult physiology. Pediatric patients differ significantly from adults and among other pediatric patients in anatomical, physiological, and pharmacological characteristics. Many centers have established a separate pediatric anesthesia subspecialty in order to meet the appropriate anesthetic requirements of

newborns, premature infants, infants, children, and adolescents. In particular, neonates carry 10 times more mortality and morbidity risk compared to other pediatric age groups. The most common complications in this age group involve the cardiovascular and respiratory system [1]. Holzman [2] noted that the practitioner's experience and the presence of existing respiratory, cardiac, or muscular disease are the key factors that determine the risk of mortality and morbidity. Hemodynamic disturbances due to hypotension, hypertension, tachycardia, bradycardia, asystole, or other arrhythmias arising in the cardiovascular system and respiratory system issues such as hypopnea, apnea, hypoxia, hypocapnia, or hypercapnia can lead to disturbances in microcirculation to the central nervous system (CNS). Although the rate of complications has been reduced through improved understanding of the anatomical, physiological, and pharmacological characteristics of pediatric patients, advances in monitoring methods, and practitioner specialization, the risks are never completely eliminated.

Despite recent advances in the field of pediatric anesthesia, an increasing number of recent reports point to the adverse effects of anesthetics on the developing brain, raising concerns about the application of anesthesia in pediatric patients. As early as 1965, Sir Austin Bradford Hill recognized this issue at a meeting of the Royal Society of Medicine, stating: "How do we determine what are physical, chemical and psychologic hazards of occupation and in particular those that are rare and not easily recognized?" and "… the available human studies … cannot exclude the possibility that the anesthesia- induced neurotoxicity observed in many animal studies may also occur in children" [3]. Although it has been nearly 50 years from that meeting of the Royal Society of Medicine, the short- and long-term effects of anesthesia applications in pediatric patients remain poorly understood. In this chapter, the acute and long-term effects of anesthesia and anesthetics on the developing brain are summarized.

2. Definitions

Neurotoxicity of anesthetic substances on the developing brain is determined by a reduction in neural density and apoptosis in experimental studies and by disturbances in memory, attention, learning, and motor activity in clinical studies [4–6]. Although anesthetic agents used in neonates have known neurotoxic effects, there are valid reasons for using these agents even in vulnerable patients. Because pain itself has a neurotoxic effect, anesthesia-analgesia application in painful conditions may have a net neuroprotective effect [7, 8]. It should also be noted that in cases of hypoxia-ischemia or trauma, administration of anesthetics reduces the infarct volume by reducing the metabolic rate, decreasing intracranial pressure, eliminating free oxygen radicals, and reducing secondary injury [9–11]. Another positive effect is neuroplasticities. These are described as the neurophysical and neurochemical ability to improve compliance against environmental changes and damage when used in depressive disorders and diseases. Neuroplasticity refers to the increase in intercellular connections. Agents that enhance neuroplasticity have raised new hope for the treatment of neurodegenerative diseases [12–14].

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3. Other factors that may cause neurotoxicity

Anesthetics are just one of many potential sources of perioperative neurotoxicities. Patient-related factors, such as genetic anomalies, prematurity, sepsis, infection, and vascular diseases, can cause perioperative toxicity. Additionally, hormonal, metabolic, inflammatory, or cardiovascular changes caused by trauma or surgery, hemodynamic disturbances, hypoxia, hypo-/hypercapnia, hypo-/hyperglycemia, electrolyte imbalances, and temperature variations that occur due to anesthesia can also contribute to the development of perioperative neurotoxicity [15–18].

4. Experimental studies

4.1. Inhalation anesthetics

In an experimental study by Shen et al. [4], sevoflurane was applied to neonatal (PND3, PND7, and PND14) and adult rats (PNW7) at concentrations ranging from 1% to 4%. Spatial memory was then assessed in adulthood using the Morris water maze (MWM) test. The PNW7 rats were less sensitive to sevoflurane than neonatal rats. Memory defects were apparent in groups treated with repeated low doses or a single high-dose anesthetic. The authors concluded that neonatal exposure to sevoflurane can result in memory defects in adulthood, with greater deficits seen in animals treated with multiple doses in a short period of time. As a result, the authors recommend that exposure to anesthesia during the neonatal period should be limited in dose and duration. Another study has shown that 4-hour sevoflurane exposure (2.5%) resulted in reduced hippocampal postsynaptic density protein-95 expression without causing any neuronal loss and was associated with learning and memory disturbances [19].

Another experimental study reported that 0.5% minimum alveolar concentration (MAC) sevoflurane applied for 6 hours had no significant effect on apoptosis and S100β levels. Conversely, isoflurane, which is given in the same circumstances, was shown to increase the level of apoptosis and S100β levels [20]. In another study, which evaluated the effects of inhalation anesthetics in neonatal rats, it was demonstrated that sevoflurane, isoflurane, and desflurane increased caspase-3 levels. Interestingly, nitrous oxide application (up to 150% concentration) for 6 hours did not cause neuroapoptosis; however, apoptosis was increased when nitrous oxide was applied with isoflurane [21]. Halothane administered during the prenatal period was associated with neurodegeneration and behavioral changes [22, 23]. Xenon, the currently preferred anesthetic, does not cause neuroapoptosis when used alone; on the contrary, xenon reduced the effects of other inhalation anesthetics when administered first [24].

4.2. Intravenous anesthetics

Zou et al. [5] have examined the effect of ketamine anesthesia duration in newborn rhesus monkeys (PND5, PND6) through silver and Fluoro-Jade C stains and caspase-3 immunostain. Three hours exposure to ketamine did not produce any significant histochemical change, whereas profound brain cell death was observed in the frontal cortex among subjects that

were under the effect of ketamine for 9 or 24 hours. In cell culture study of Bosnjak et al. [25], they demonstrated that ketamine decreases neuronal viability time and dose dependently, leads to neuronal ultrastructural abnormalities, causes depolarization of mitochondrial membrane potential, induces apoptotic pathway, causes cytochrome c release from mitochondria into cytosol, and induces free oxygen radical production.

Yu et al. examined neuroapoptosis and long-term behavioral changes in PND7 rats that were given single and repetitive doses of propofol. Their findings included reduction in neuron density, morphological changes in pyramidal cells, apoptosis, and suppressed release of excitatory neurotransmitters. Additionally, these effects were more pronounced among the group that was subject to repeated doses of propofol [26].

Benzodiazepines (clonazepam, diazepam, and midazolam), which are intravenous anesthetics, have controversial effects on apoptosis; however, barbiturates (pentobarbital, phenobarbital) clearly increase apoptosis. The few studies that have examined the effects of sodium thiopental reported that exposure did not result in increased apoptosis [27–33]. Thompson [34] has suggested high-dose narcotic anesthetic for neonatal and infant. But, fetal and neonatal chronic exposure to opioids has been associated with neuronal changes. Although opioid-based anesthesia and opioids coadministered with inhalation anesthetics have been shown to reduce apoptosis, safety has not been demonstrated with these preparations [35, 36]. However, these studies are controversial and their safety has been in question. Another study has demonstrated that dexmedetomidine, the current intravenous anesthetic, reduces prenatal toxicity caused by propofol [37].

5. Pathogenesis

The molecular pathogenesis of anesthesia-induced neurotoxicity has also been investigated in experimental studies.

Neonates are born with approximately 100 billion neurons, and the number of neurons does not increase over time. The neonatal brains weigh approximately 300–400 g. Increased myelination, synapse formation, neuron maturation, and proliferation of glial cells increase the weight of the brain to 1100 g at 3 years of age and 1300–1400 g at adulthood. A newborn infant has approximately 50 trillion synapses, increasing to 1000 trillion within the first year of life and decreasing to 500 trillion in adulthood. Critical periods for brain development are the intrauterine period, the first 3 years of life and puberty [38–40].

Thus, brain maturation is not complete at birth, and there is a heterogeneous maturation process in the brain following birth. Maturation is particularly slow in the cortex and in the limbic system [38–40]. Alteration of neurotransmission in the immature brain due to anesthesia exposure may lead to future impairments.

Synaptogenesis has been defined as the most important period of brain development, also described as the “fragile period” or “critical period.” Synaptogenesis consists of five phases. The greatest leap in synapse formation occurs in phase 3, which is sometimes referred to as

the "big bang." Phase 3 corresponds to the neonatal period. Following phase 3, synaptogenesis continues with the same speed during phase 4. This phase is referred to as the plateau phase, corresponding to infancy and adolescence. During phase 5, which occurs during adulthood, synaptogenesis continues, but it is limited and localized [41]. The initiation, duration, and end of these critical periods (phase 3 and phase 4) are controlled by multiple genetic and epigenetic mechanisms. The brain's sensitivity to environmental stimuli is at maximum during the neonatal and infancy period when synaptogenesis is also maximized [41].

Anesthetics elicit their effects by enhancing the activity of major inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine or antagonizing the N-methyl-D-aspartate (NMDA) receptors of the major excitatory neurotransmitter glutamate. During brain development, GABA facilitates cell proliferation, neuroblast migration, and dendritic maturation, and unlike in adults, it acts as an excitatory neurotransmitter during infancy rather than an inhibitory neurotransmitter [42, 43]. This is because these two mediators increase the permeability of the cell membrane to chloride ions through intrinsic chloride-conducting ion pores. After the permeability of the GABA, ligand-gated ion channel to chloride is increased, KCC2 K+/Cl-2 cotransporter aids in influx of chloride ion. Thus, the neuron is hyperpolarized and its activity is suppressed. However, because KCC2 expression is low during the early period of development, the chloride action potential is reversed by $GABA_A$ and glycine receptor activity, leading to neuronal depolarization and increased permeability to chloride. Clinical studies have shown that sevoflurane, isoflurane, and propofol cause excitability in electroencephalogram in neonates [44–46]. The major excitatory neurotransmitters glutamate and aspartate are present in the brain at very high concentrations (glutamate 10 mmol/L and aspartate 4 mmol/L). Glutamate and aspartate direct synaptic signaling at nerve terminals and control ion intake to neurons. They have been found to influence synaptogenesis, neuronal plasticity, learning, and memory [47–49]. Although the excitatory neurotransmitters are normally responsible for nerve conduction, they are also potential sources of neurotoxicity. An abnormal decrease in glutamate may disturb normal excitation, and abnormal increases may cause excitotoxicity and cell death by disturbing calcium homeostasis. Glutamate and similar amino acids have been shown to cause acute swelling in the neuron body, dendrites, and glia and also promote neuronal degeneration over extended periods of time. For this reason, there is a delicate mechanism acting in normal conditions to regulate glutamate levels in the synaptic gap involving reuptake of excess glutamate from the synaptic gap through receptors present in presynaptic end of nerve terminal and glial cells. Although glutamate is a strong and rapid-acting toxin under physiological conditions, this mechanism ensures that even direct application to the brain does not cause damage [47]. Nevertheless, pathological conditions that result in insufficiency of this system or cause release of large amounts of glutamate would lead to neuronal loss. For these reasons, anesthesia applications are believed to disrupt the balance between excitatory and inhibitory neurotransmission and thus cause neuronal injury [47–49].

Regarding neuronal viability and development, one of the most studied neurotropins in neonatal subjects is brain-derived neurotrophic factor (BDNF). Mature BDNF is formed by destruction of proBDNF in the synaptic gap by the action of plasmin. Mature BDNF binds to the TrkB receptors present on the postsynaptic membrane and enhances viability of the target

cell. However, in conditions where plasmin release is reduced or blocked, such as when anesthesia is applied, proBDNF cannot be converted to the mature form, and it stimulates p75NTR instead of the TrkB receptor. Activation of p75NTR receptor, also called the "death receptor," leads to actin depolymerization and apoptosis. Head et al. [50] demonstrated that isoflurane causes apoptosis in the neonatal mice brain through this pathway.

Apoptosis is a programmed cell death that can occur in both physiological and pathological conditions. Apoptosis is physiologically present in the developing brain, occurring at a rate of approximately 1%. However, apoptosis that occurs following pathological processes like hypoxia and ischemia is typically problematic. Several experimental studies have shown that apoptosis is increased following anesthesia exposure. However, it is not possible to conduct such studies in humans. Therefore, it is difficult to estimate the rate of apoptosis following anesthesia exposure in humans to what extent this apoptosis affects maturation of the developing brain. Experimental studies have shown that anesthesia induces apoptosis via intrinsic and extrinsic pathways. Anesthesia application causes leakage of cytochrome c and translocation of Bax protein to the mitochondria, leading to activation of the apaf-1 and caspase pathways, respectively. This in turn results in lipid peroxidation via release of free oxygen radicals. Apoptosis occurs not only in intrinsic pathway but also in extrinsic pathway which activates Fas protein [51–53].

There are three publications that demonstrate the relationship between microRNA and anesthetic-induced developmental neurotoxicity; according to these publications, while propofol downregulates microRNA-21, ketamine upregulates microRNA-34a, microRNA-34c, and microRNA-124 and downregulates microRNA-137 [54–56].

In cell culture models, it has been demonstrated that neuron development is highly dependent on the actin cytoskeleton, and anesthetics are dangerous for actin regulation [57–59].

Tau protein hyperphosphorylation at serine 404 demonstrates neurodegeneration and is induced by ketamine. Therefore, microtubules are disrupted and damaged [60].

Translocator protein (TSPO, 18 kDa) is a biomarker that could be used for evaluation of reactive gliosis and microglia activity and has the potential for use in noninvasive imaging using positron emission tomography and single photon emission computed tomography [61]. The relationship between anesthesia-associated neurotoxicity and DNA methylation and gene expression has been investigated [62].

Treatment strategies to reduce neurodegeneration induced by anesthetics have also been widely investigated. Lithium, melatonin, estradiol, pilocarpine, dexmedetomidine, xenon, erythropoietin, L-carnitine, hydrogen gas, and pramipexole are among the leading candidates for this emerging therapy [63, 64].

6. Clinical studies

Although many experimental studies have been conducted, this alone is not sufficient evidence to conclude that general anesthetics have a neurotoxic effect on the developing human

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brain. Even within mammals, species vary widely in the rate and timing of brain development. Total maturation of the brain takes only a few weeks in the rat, while maturation of the human brain occurs over many years. In addition, the dose and duration of anesthetics used in experimental models is not directly proportional to the procedures used in patients. In some cases, experimental doses may be as much as 20 times the standard clinical dose. Adjusted for the life span of a rat, 6 hours of anesthesia may correspond to 1 month of a human life span. Again, some observations from these studies, such as lactic acidosis, hypercarbia, and hypoglycemia, have mostly been ignored. Learning ability is also disturbed in subjects that are fasted for the duration of the anesthesia treatment [43, 65, 66].

In one retrospective birth cohort study that used New York State Medicaid data collected between the years 1999 and 2002, 383 children who underwent inguinal hernia repair with anesthesia before the age of 3 were evaluated along with 5050 children who did not undergo an operation. Hazard ratios regarding behavioral and developmental disorders were reported to be 2.3 with exposure to anesthesia, 1.0 for age, 2.7 for gender, 1.2 for race, and 1.6 for birth complications [6]. Considering that elective surgeries can be postponed, exposure to anesthesia is an avoidable risk for most infants.

In another report, patients that had been overexposed to anesthesia had more learning difficulties than those who were treated with appropriate doses. The risk of learning difficulties was progressively increased with repeated exposure to anesthesia [67, 68]. The effects of anesthesia used during cesarean procedures were examined in children. Infants born under regional anesthesia exhibited fewer learning difficulties in the later stages of their life [69, 70].

One retrospective study examined 10,450 siblings born between the years 1999 and 2005 and evaluated developmental and behavioral disorders among those who did and did not receive anesthesia prior to the age of 3. The incidence of developmental and behavioral disorder was 128.2/1000/year among those who were exposed to anesthesia and 56.3/1000/year among those who were not exposed to anesthesia. Therefore, behavioral disorders were 60% more frequent among those who received anesthesia in comparison to those who did not. The estimated hazard ratio for developmental and behavioral disorders was 1:1 for those who received anesthesia once before the age of 3, 2:9 for those exposed twice, and 4 for those who had been exposed to anesthesia three or more times [71].

Meyer et al. observed development of convulsion with similar clinical characteristics in three infants under the age of 2 months, occurring after 23–30 hours of anesthesia induced and maintained using propofol. They reported that the seizures did not recur; however, two infants had progressive microcephaly and cognitive and behavioral disorder. Magnetic resonance imaging also showed white matter abnormalities [72]. The manufacturer of propofol does not recommend the use of propofol as a general anesthetic agent for children under the age of 3 [73].

Clinical studies in the literature are often retrospective, and even strong correlations are not evidence of causality. Therefore, the Mayo Anesthesia Safety in Kids (MASK) study was launched by Mayo Clinic at the suggestion of the FDA to evaluate neurotoxicity in children exposed to anesthesia. The study included children born in Olmsted County between 1997 and 2007 and who still lived there when they reached 8 years old. Those who received general

anesthesia before the age of 3 were excluded from the study. Children classified as having single, multiple, or no anesthesia exposure were evaluated between the years 2007 and 2016, when they were at the age of 8–12 or 15–19 with a single session that lasted for 4 hours using the National Center for Toxicological Research-Operant Test Battery (NCTR-OTB). The NCTR-OTB test evaluates processing speed; cognitive/intellectual memory; attention, language, motor and visual-spatial, and cognitive processing; and executive functions [74].

The Pediatric Anesthesia and Neurodevelopmental Assessment (PANDA), which was conducted by the University of Columbia and followed sibling pairs under the age of 3 who underwent inguinal operation up to the age of 8–15, published four symposiums in 2-year interval. The first meeting in 2008 established the goals of the study. The second meeting in 2010 was interdisciplinary. The third meeting in 2012 was attended by different disciplines, parents, clinicians, FDA workers, and patient's rights advocates. In this meeting, attendees agreed to collaborate on advanced preclinical, clinical, and translational studies [75, 76]. Additionally in 2012, pediatric anesthesiologists and pediatric surgeons met to discuss the neurotoxicity risk of some elective procedures and anesthesia applications performed in children and specifically to discuss questions and concerns of parents. Meeting attendees, including pediatric general surgeons, urologists, plastic surgeons, and ophthalmologists, reviewed inguinal hernia, hypospadias-undescended testis, cleft lip, craniosynostosis, cataracts, and strabismus applications in early childhood. They emphasized that the amount of volatile anesthetics and sedation levels could be reduced by using balanced anesthesia methods, regional anesthesia methods, and the use of opioid and non-opioid analgesics, but the group was unable to reach a consensus on best practices [77]. At the 2014 meeting, the existing clinical studies, General Anesthesia Study (GAS), MASK, and PANDA, were evaluated, and Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots (SmartTots) was presented along with the future targets of this organization. SmartTots is a public-private partnership that investigates the effects of anesthetic agents on neural development in infants and children. All panelists evaluated their anesthesia and clinical practices with the following questions [78, 79]:

- What does anesthesia mean to my patients?
- What does anesthesia mean to my practice now?

Ordering imaging studies with sedation/anesthesia.

A child requiring multiple procedures under GA overtime.

A child requiring multiple procedures from different subspecialties at the same time.

- If anesthesia affects neurodevelopment:

How will I discuss this with the parents?

Will I change my practice and how?

The 2014 report indicated that the collected data was insufficient to draw any conclusions. However, it stated 2 years later that the results would be considered as a public health problem, leading to greater awareness [78]. On the other hand, the General Anesthesia Study

(GAS), which is currently ongoing and only investigates causality, investigated cases that were less than 60 weeks from conception and greater than 26 weeks gestational age and had undergone inguinal hernia operations with sevoflurane-based general anesthesia or awake-regional anesthesia. This study was conducted in 28 hospitals from Australia, Italy, the USA, the UK, and Canada. No opioids or nitrous oxide was used. Regional techniques and intravenous acetaminophen were used for postoperative analgesia. Protocols were applied in order to prevent development of adverse states that would contribute in neurotoxicity, such as hypoglycemia, hypotension, and hypoxia. Children were assessed using the composite cognitive score of the Bayley Scales of Infant and Toddler Development III test at the age of 2 and with the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at the age of 5. During 2007–2013, 363 infants were enrolled in the awake-regional group, and 359 infants were enrolled in the general anesthesia group. According to the study results, the median general anesthesia duration was 54 minutes. No significant difference was found between the groups regarding cognitive composite score at 2 years of age. This study provides strong evidence that sevoflurane anesthesia lasting <1 hour in infants does not produce more severe neurotoxicity at the second year of age than awake-regional treatment. Nonetheless, the primary outcome of this study is the evaluation of neurodevelopmental state at 5 years of age, and this result has not been published yet. It was also reported in this study that early-period apnea development (<30 minutes) was less frequent in the regional anesthesia group [80].

Other discussed topics are applied anesthesia techniques to mothers during childbirth. Flick et al. determined that neuraxial labor analgesia for vaginal delivery did not cause learning disabilities in childhood [69, 70].

Another topic of discussion was how parents should be informed and the need to establish a protocol. However, since it was not possible to reach a consensus based on the current data, it was concluded that it would not be appropriate to inform parents and establish a protocol yet [81].

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